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NUCALA® (mepolizumab) for Treatment of Patients with Severe Asthma with Eosinophilic Inflammation

BLA125526

FDA Advisory Committee Meeting Briefing Document

Presented to:

Pulmonary-Allergy Drug Advisory Committee

Document Date: May 7, 2015

Advisory Committee Meeting: June 11, 2015

ADVISORY COMMITTEE BRIEFING MATERIALS

AVAILABLE FOR PUBLIC RELEASE

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ABBREVIATIONS

ACQ-5	Asthma Control Questionnaire-5 items
ACQ-6	Asthma Control Questionnaire-6 items
ACT	Asthma Control Test
ADA	anti-drug antibody
AE	adverse event
ALT	alanine aminotransferase
AM	morning
AQLQ	Asthma Quality of Life Questionnaire
AST	aspartate aminotransferase
ATS	American Thoracic Society
AUC	area under the plasma concentration time curve
BAL	bronchoalveolar lavage
BDP	beclomethasone dipropionate
BLA	Biologics License Application
BMI	body mass index
bpm	beats per minute
CBC	complete blood count
CI	confidence interval
Cmax	time to maximum concentration
CMH	Cochran-Mantel-Haenszel
COPD	chronic obstructive pulmonary disease
CV	cardiovascular
CVT	cardiac, vascular, and thromboembolic
ECG	electrocardiogram
ED	emergency department
EGPA	eosinophilic granulomatosis with polyangiitis
ERS	European Respiratory Society
FAAN	Food Allergy and Anaphylaxis Network
FDA	Food and Drug Administration
FeNO	exhaled nitric oxide
FEV_1	forced expiratory volume in 1 second
FP	fluticasone propionate
FVC	forced vital capacity
GGT	glutamyl transferase
GINA	Global Initiative for Asthma
GSK	GlaxoSmithKline
hERG	human ether-a-go-go related gene
ICS	inhaled corticosteroid(s)
ICU	intensive care unit
ID_{50}	dose associated with 50% of the maximal inhibition effect
ID_{90}	dose associated with 90% of the maximal inhibition effect
IgE	immunoglobulin E
IgG	immunoglobulin G
IL-5	interleukin-5
IND	Investigational New Drug application

ISAAC	International Study of Asthma and Allergies in Childhood
ITT	Intent-to-Treat
IV	intravenous
J2R	Jump to Reference
kg	kilogram
L	liter
LABA	long-acting beta-2 receptor agonist
LTRA	leukotriene receptor antagonist
m	meter
mAb	monoclonal antibody
MAR	Missing at Random
MCID	minimal clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mL	millilitre
MMRM	mixed model repeated measures
msec	millisecond
NAb	neutralizing antibody
NIAID	National Institute of Allergy and Infectious Disease
NICE	National Institute for Health and Care Excellence
NIH	National Institutes of Health
NHLBI	National Heart, Lung and Blood Institutes
OCS	oral corticosteroid(s)
OLE	Open-label Extension (Studies)
OR	odds ratio
PD	pharmacodynamic
PEF	peak expiratory flow
PK	pharmacokinetic
ppb	parts per billion
QTc	corrected QT interval
QTc(F)	corrected QT interval using Fridericia's formula
RCT	Randomized Controlled (Studies)
SAE	serious adverse event
SARP	Severe Asthma Research Program
SC	subcutaneous
SD	standard deviation
SGRQ	St. George's Respiratory Questionnaire
SMQ	standard MedDRA query
SOC	System Organ Class
t1/2	terminal half life
Th2	T helper 2
Tmax	time to maximum concentration
µL	microliters
UR	Unconditional Reference
URTI	upper respiratory tract infection
US	United States
Yr	year

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1. EXECUTIVE SUMMARY

Background: Mepolizumab (SB-240563) is a humanized monoclonal antibody (immunoglobulin G [IgG1], kappa, monoclonal antibody [mAb]) that has been developed as an add-on maintenance treatment for patients with severe asthma with eosinophilic inflammation. Severe asthma is defined as asthma that requires treatment with high-dose inhaled corticosteroids (ICS) plus a second controller (and/or systemic corticosteroids) to prevent it from becoming uncontrolled or that remains uncontrolled despite this therapy [Chung, 2014]. Patients who remain uncontrolled suffer from limited control of symptoms, frequent exacerbations, and compromised quality of life. Exacerbations are particularly disabling for the patient and typically require treatment with high doses of systemic corticosteroids, which have well known detrimental side effects, and may require hospital admission. Studies in the severe asthma population have shown that more than half of these patients have persistent eosinophilic airway inflammation despite corticosteroid therapy [Wenzel, 2005; Chung, 2014] and there is an increasing recognition of different phenotypes, including a severe eosinophilic asthma phenotype [Chung, 2014].

Eosinophilic inflammation is promoted by T-helper 2 (Th2) cytokines. Mepolizumab binds with high specificity and affinity to human interleukin 5 (IL-5), the key Th2 cytokine responsible for regulation of blood and tissue eosinophils. Neutralization of IL-5 with mepolizumab reduces eosinophilic inflammation in the airways [Flood-Page, 2003] which leads to a reduction of exacerbations and improved asthma control.

Target Population: The target patient population most likely to benefit from mepolizumab treatment was identified through the clinical development program. The following characteristics describe a patient with severe asthma and with markers of eosinophilic inflammation: an eosinophilic phenotype with blood eosinophil threshold levels ≥150 cells/μL blood eosinophils at treatment initiation (determined from complete blood count [CBC]) *or* blood eosinophil count of ≥300 cells/μL in the 12 months prior to treatment initiation; receiving maximal standard of care treatment per National Institutes of Health (NIH) guidelines (i.e., high dose ICS plus at least one additional controller with or without continuous oral corticosteroids [OCS]). Patients in the Exacerbation Studies had a history of exacerbations. In the mepolizumab program, the above characteristics were utilized to define patients with severe eosinophilic asthma.

Clinical Development Program: The core Phase II-III clinical development program for mepolizumab in asthma was comprised of 9 studies and over 1500 patients. Mepolizumab was administered once every 4 weeks in all studies. Four Phase IIa studies (Moderate Asthma Study 006, Proof-of-Concept Studies 184 and 046 [both investigator-sponsored], and Dose-ranging Pharmacokinetic [PK]/Pharmacodynamic [PD] Study 092) provided information important to the development of mepolizumab in severe eosinophilic asthma with regard to the target population, key endpoints (exacerbation reduction and oral corticosteroid [OCS] reduction), and dose selection.

Five key studies, which are the focus of this Briefing Document, provide the primary support for the efficacy and safety of mepolizumab in severe eosinophilic asthma.

Studies 997, 588, and 575 were randomized, double-blind, parallel-group, placebo-controlled multicenter trials; Studies 666 and 661 are open-label extension studies.

- Exacerbation Study 997 was a 52-week dose-ranging (75, 250, 750 mg IV) study that confirmed the exacerbation effect seen in the Proof-of Concept Study 184, informed on the dose to take further into Phase III (75 mg IV), and informed on the clinical and blood biomarkers that predict response to mepolizumab.
- Exacerbation Study 588 was the first study to target patients based exclusively on the clinical and blood biomarkers derived from Study 997. Study 588 reconfirmed the exacerbation reduction effect of mepolizumab and showed that doses of 75 mg IV and 100 mg SC had a comparable effect. This 32-week study also provided efficacy data on quality of life, asthma control, and lung function.
- OCS Reduction Study 575, informed by the Proof-of Concept Study 046, included only the 100 mg SC dose and was the second study to target patients utilizing the clinical and blood biomarkers derived from Study 997. In addition to confirming the ability of mepolizumab to allow reduction of daily OCS (prednisone) dose, this 24-week study also reported efficacy data for quality of life, asthma control, and lung function.
- Open-Label Extension (OLE) Studies 666 (~3.5 years; ongoing) and 661 (52 weeks; concluded) enrolled patients who participated in Study 997 and in Studies 588 and 575. The OLE Studies provide additional long-term safety data for mepolizumab 100 mg SC, the proposed dose for marketing.

Study Population: The population enrolled in Exacerbation Studies 997 and 588 was representative of patients with severe eosinophilic asthma. The majority of patients were White (84%) and female (60%), the mean age was approximately 50 years, and patients tended to have an elevated body mass index (28 kg/m^2). Patients of African descent comprised 3% of the total population in the Exacerbation Studies, and of the patients enrolled at United States (US) sites, 25% were African-American. The proportion of adolescent (ages 12-17) patients enrolled in the Exacerbation Studies was small (2%), most likely because the eosinophilic-driven phenotype is more common in adults [Moore, 2010]. The population enrolled in the OCS Reduction Study 575 had similar demographic characteristics to the Exacerbation Studies, but no patients of African heritage participated. Although enrollment of adolescents and patients of African heritage was low, these subgroups showed a similar treatment response and safety profile compared with the overall population. In addition, following either IV or SC administration, both subgroups displayed plasma concentrations and predicted clearance within the range of the rest of the study population.

Patients enrolled in the Exacerbation and OCS Reduction Studies had a mean duration of asthma of approximately 19 years, suggesting many had adult onset asthma. Despite being treated with high dose ICS plus an additional controller medication (and some with daily OCS), patients had history of frequent exacerbations with a mean of ≥3 per year and baseline mean blood eosinophil counts between 230 to 290 cells/μL. This is consistent with the median blood eosinophilic counts from other cohorts in severe asthma [Schleich, 2014; Amelink, 2013]. The mean percent predicted forced expiratory volume in 1 second

(FEV_1) was approximately 60% and FEV_1/forced vital capacity (FVC) ratio was low (~0.64), which is consistent with severe disease [Chung, 2014]. Mean baseline Asthma Control Questionnaire (ACQ-5) scores were 2.0 to 2.4 which are greater than the threshold of 1.5 indicating uncontrolled disease [Juniper, 2006]. In the Exacerbation Studies, over one third of the patients (39%) required an emergency department (ED) visit or hospitalization due to an exacerbation in the previous year.

Efficacy Results: Add-on treatment with mepolizumab is efficacious in patients with severe eosinophilic asthma who are receiving standard of care therapy as demonstrated by the Phase II/III program. In Studies 997 and 588, mepolizumab consistently demonstrated ~50% reduction in exacerbations (primary endpoint of the studies), ~40% reduction in more severe exacerbations requiring ED visits *and/or* hospitalization, and ~50% reduction in serious exacerbations requiring hospitalization only.

Improvements in asthma control (ACQ-5) and lung function (FEV_1) were observed with mepolizumab in all three studies although the magnitude of effect was not consistent. For the ACQ-5, small improvements less than the minimal clinically important difference (MCID) of -0.5 were observed for mepolizumab compared with placebo in Study 997 (-0.15 to -0.28); however in Study 588 (-0.42 and -0.44) and in Study 575 (-0.52), point estimates of differences from placebo approached or exceeded the MCID. Compared with placebo, improvements in pre-bronchodilator FEV_1 were less marked with mepolizumab in Study 997 (56 to 81 mL); however, in Studies 588 and 575, statistically significant and clinically relevant improvements were observed (98 to 114 mL). It is possible that the improvements in these endpoints in Study 588 are related to the refined selection criteria with the use of the blood eosinophil biomarker. In Studies 588 and 575, improvements in quality of life (St. George's Respiratory Questionnaire [SGRQ]) were demonstrated with mepolizumab; point estimates of differences from placebo were statistically significant and exceeded the MCID of -4.0 for the instrument (-5.8 to -7.01). Small improvements were seen with the Asthma Quality of Life Questionnaire (AQLQ) instrument in Study 997.

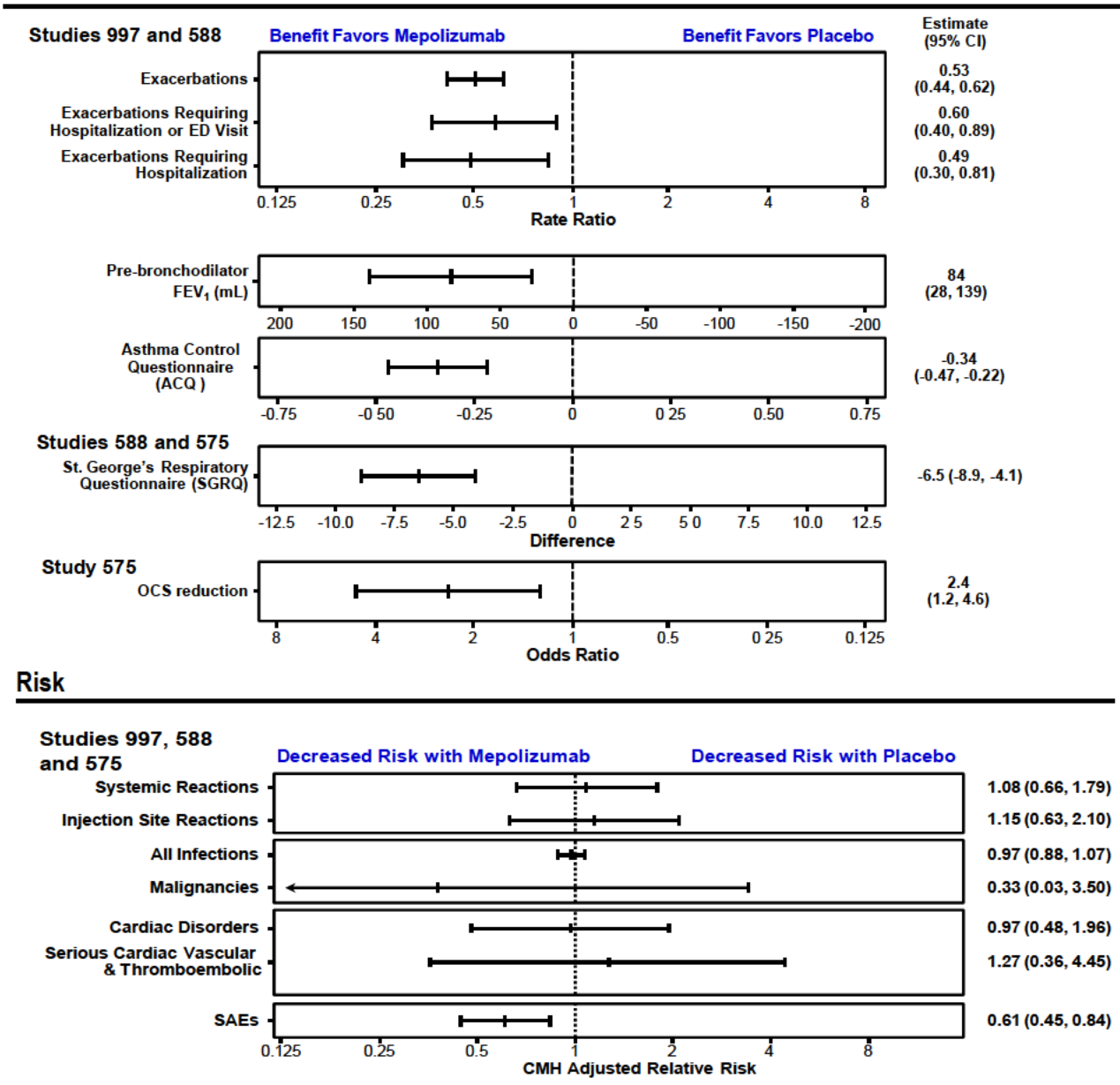
In Study 575, mepolizumab significantly reduced the need for daily OCS, while maintaining and improving asthma outcomes compared with patients in the placebo group who continued to receive higher doses of OCS. At the end of the treatment period, the median daily dose of prednisone was reduced from 10 mg to 3.1 mg in the mepolizumab group, but only from 12.5 mg to 10 mg in the placebo group.

Safety Results: The overall adverse event (AE) profile of mepolizumab was consistent across the severe eosinophilic asthma program and similar to the profile in patients receiving placebo (standard of care). The incidence of local injection site reactions following SC administration of mepolizumab was relatively low although higher than placebo (8% vs. 3%); no reaction was severe or serious. The profile of AEs of special interest (i.e., systemic [hypersensitivity/non-allergic] reactions, immunogenicity, infections, neoplasms, and cardiovascular events) was comparable to placebo and none have been associated with an increased risk following mepolizumab treatment. No events of anaphylaxis have been attributed to mepolizumab. The incidence of anti-drug antibodies (ADA) with SC administration of mepolizumab was 6% compared with 1% for placebo. Only one patient developed neutralizing antibodies and this case was not

associated with hypersensitivity. There were no clinically relevant effects on vital signs, corrected QT (QTc) interval, or clinical laboratory tests associated with mepolizumab treatment. Even with up to 3 years of exposure (median of 18.2 months) across the Phase III studies (at the time of data cut-off for the 120 Day Safety Update), the safety profile of mepolizumab has remained consistent with that reported in the original Biologics License Application (BLA).

Benefit/Risk: The efficacy and safety data provide strong evidence of drug effectiveness, a well-characterized safety profile, and overall positive benefit to risk profile for mepolizumab 100 mg SC as an add-on treatment for severe eosinophilic asthma (Figure 1). Based on the limitations associated with current therapeutic treatment options, and the significant morbidity experienced by patients with severe eosinophilic asthma, there is an urgent medical need for additional therapeutic options.

Figure 1 Benefit Risk Profile of Mepolizumab in Severe Eosinophilic Asthma



2. INTRODUCTION

Mepolizumab (SB-240563) is a humanized anti-IL-5 monoclonal antibody (IgG1, kappa, mAb) that has been developed as an add-on maintenance treatment for patients with severe asthma with eosinophilic inflammation. Mepolizumab reduces eosinophilic inflammation of the airways [Flood-Page, 2003], which leads to reduction of asthma exacerbations in patients who experience frequent exacerbations. Mepolizumab improves asthma control and quality of life and allows for reduction of daily OCS dose in OCS-dependent patients. The safety profile of mepolizumab is similar to standard of care.

The target patient population most likely to benefit from mepolizumab treatment was identified through the clinical development program. The following characteristics describe a patient with severe asthma and with markers of eosinophilic inflammation: an eosinophilic phenotype with blood eosinophil threshold levels ≥150 cells/μL blood eosinophils at treatment initiation (determined from CBC) *or* blood eosinophil count of ≥300 cells/μL in the 12 months prior to treatment initiation; receiving maximal standard of care treatment per NIH guidelines (i.e., high dose ICS plus at least one additional controller with or without continuous OCS). Patients in the Exacerbation Studies had a history of exacerbations. In the mepolizumab program, the above characteristics were utilized to define patients with severe eosinophilic asthma.

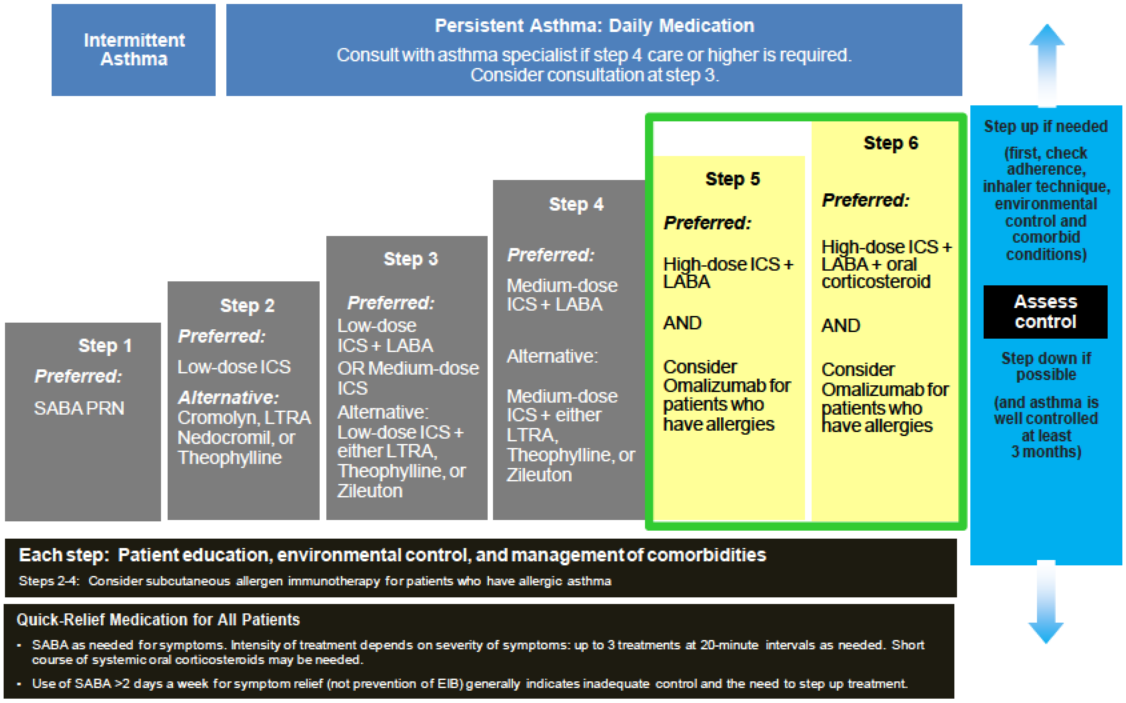
2.1. Severe Asthma and Unmet Medical Need

Asthma is a heterogeneous chronic lung disease characterized by inflammation, narrowing of the airways, and reversible airway obstruction. In the US, asthma affects an estimated 25.6 million individuals, including 18.7 million adults (age ≥18 years) [Blackwell, 2014], 2.6 million adolescents (age 12-17 years), and 3.2 million children (age 5-11 years) [Bloom, 2013]. Clinical manifestations of asthma include frequent symptoms of shortness of breath, cough and wheeze and unpredictable acute worsening of symptoms (exacerbations). Patients with uncontrolled severe asthma suffer from limited control of symptoms, frequent exacerbations, and compromised quality of life. Exacerbations are particularly disabling for the patient and typically require treatment with high doses of systemic corticosteroids and may require hospital admission.

The morbidity and mortality associated with asthma presents a substantial social and economic burden including direct medical costs and indirect costs due to lost productivity. Although patients with uncontrolled severe asthma represent less than 5% of the total asthma population [Barnes, 1996], these patients experience considerable morbidity [Polosa, 2008] and are responsible for approximately 50% of total health care costs associated with asthma [Cisternas, 2003]. Epidemiological studies show that 34% of patients with severe asthma are hospitalized at least once in a 12 month period, more than 50% have at least one urgent care visit per year, 54% require at least three prednisone courses per year, and nearly 25% have had a near fatal event in their life time [Moore, 2007; Carvalho-Pinto, 2012].

The majority of patients with asthma can be adequately controlled by following step-wise treatment recommendations [GINA, 2013; NIH, 2007] (Figure 2). However, some patients with severe asthma continue to experience uncontrolled disease despite maximal therapy (e.g., Step 5 and 6 - high dose ICS plus additional controller medications). Preventing the future risk of an exacerbation is a key goal of an asthma management plan.

Figure 2 Stepwise Approach to Managing Asthma in Patients 12 Years of Age and Older



Key ICS, inhaled corticosteroid; LABA, inhaled long-acting beta$_2$-agonist; LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting beta$_2$-agonist

***Guidelines for the Diagnosis and Management of Asthma (EPR-3) 2007*. NIH, NHLBI. August 2007. NIH publication no. 07-4051.**

Corticosteroids are considered the most effective anti-inflammatory treatments for all severities of persistent asthma [GINA, 2013]. The American Thoracic Society/European Respiratory Society (ATS/ERS) Task Force [Chung, 2014] for severe asthma recommends that control should first be attempted through the use of high-dose ICS before adding daily OCS or omalizumab (for the subgroup of patients with elevated immunoglobulin E [IgE] and who are allergic to a perennial allergen).

Use of OCS on a regular basis have well-documented side effects. Short-term effects of OCS therapy include increased risk of glaucoma, hypertension, sleep disturbances, mood swings, and weight gain. With long-term use of OCS, there is increased risk of cataracts, diabetes, infections, osteoporosis, fractures, suppressed adrenal gland hormone production, and skin thinning [Manson, 2009]. For adolescent patients, growth impairment is also a concern. In addition, withdrawal effects can potentially be life threatening (e.g., Addison's disease). A recent study by Lefebvre and colleagues using Medicaid insurance claims data from 3628 patients with asthma and more than 6 months of continuous OCS use (low ≤6 mg/day, medium >6-12 mg/day, and high >12 mg/day) was reported [Lefebvre, 2015]. Patients with medium and high steroid exposure had higher risk for developing cardiovascular complications (Odds ratio [OR]: 2.12 [95% CI: 1.63-2.76] and 1.96 [95% CI: 1.48-2.58]), infections (OR: 1.72 [95% CI: 1.37-2.16] and 1.91 [95% CI: 1.51-2.43]), and gastrointestinal complications (OR: 1.63 [95% CI: 1.34-1.99] and 1.81 [95% CI: 1.46-2.24]), respectively, compared with patients with low steroid exposure. For these reasons, physicians and patients are reluctant to use OCS on a regular basis to control their asthma and even short-term to treat exacerbations.

Consequently, it is not surprising that adherence to daily OCS has been documented to be as low as 50% [Robinson, 2003; Gamble 2009].

Omalizumab, a recombinant humanized anti-IgE mAb (IgG1) is recommended for use in GINA Step 5/NIH Steps 5 and 6 (add-on treatment for allergic asthma), but only a small proportion of patients with severe asthma are appropriate candidates for its use based on specific body weight and circulating IgE levels in addition to a positive test for a perennial allergen. A recent report of patients with severe asthma found that after applying the National Institute for Health and Care Excellence (NICE) guidelines, only 6.2% of patients with severe asthma qualified for omalizumab use [Agbetile, 2011]. When the omalizumab label criteria were applied to the severe eosinophilic asthma population, there was an approximately 30% overlap with the mepolizumab target population in Study 997.

Studies using existing steroid-sparing treatments such as methotrexate [Shiner, 1990; Davies, 2000], cyclosporine [Lock, 1996; Nizankowska, 1995], and oral gold [Evans, 2001] have demonstrated variable and marginal effects on OCS reduction and significant toxicity. Use of these agents is not recommended in the current treatment guidelines because of their poor risk/benefit ratio [GINA, 2013]. In addition, due to the undesirable safety profile of OCS and the limited application of omalizumab in severe asthma [Normansell, 2014], there are few treatment options to reduce the frequency of exacerbations and the dependence on systemic corticosteroids for patients with severe asthma. Thus, there remains a high unmet need to provide alternative treatment options, without the side effects associated with systemic corticosteroids, for this small segment of the asthma population.

2.1.1. Severe Eosinophilic Asthma Phenotype

An extensive NIH-supported research effort found that patients with asthma can be phenotypically grouped into 5 different heterogeneous clusters of increasing severity [Moore, 2010]. This is the largest research effort of this type and is US based. Clusters 1 and 2 characterize patients with mild-to-moderate allergic asthma; Clusters 3 through 5 represent phenotypic profiles associated with more severe disease (Figure 3). While many of the phenotypic traits are unique across the three severe clusters, airway eosinophilia is a common marker across these subgroups. Evidence shows that patients with severe asthma are comprised of complex, overlapping and non-overlapping phenotypes, including a severe eosinophilic asthma phenotype [Chung, 2014].

Figure 3 Heterogeneity and Complexity in Asthma

Cluster 1 Mild Allergic Asthma	Cluster 2 Mild-Moderate Allergic Asthma	Cluster 3 More Severe Older Onset Asthma	Cluster 4 Severe Variable Allergic Asthma	Cluster 5 Severe Fixed Airflow Asthma
• Early onset	• Early onset	• Very late onset	• Early onset	• Older; long duration
• Atopic • Normal lung function	• Atopic • Borderline low FEV_1	• Less atopic • Slightly decreased FEV_1 reversibility • Obese	• Atopic • Severely decreased FEV_1 but near-normal reversibility • High symptoms and albuterol use	• Less atopic • Severely decreased FEV_1 with less reversibility • High symptoms and albuterol use despite OCS
• ≤2 asthma controllers	• ≤2 asthma controllers	• Frequent OCS use despite ≥3 asthma controllers & high-dose ICS	• Frequent OCS use	
• Minimal healthcare utilization	• Low healthcare utilization		• High healthcare utilization	• High healthcare utilization
• Minimal sputum eosinophilia	• Minimal sputum eosinophilia	• Sputum eosinophilia & neutrophilia	• Sputum eosinophilia	• Sputum eosinophilia & neutrophilia

Adapted from Moore et al. Am J Resp Crit Care Med 2010;181:315-323.

Studies in the severe asthma population have shown that more than half of these patients have persistent eosinophilic airway inflammation despite corticosteroid therapy [Wenzel, 2005; Chung, 2014]. Eosinophilic asthma can be associated with increased asthma severity, atopy, late-onset disease, and steroid insensitivity [Werner, 2013; Walford, 2014]. Eosinophilic airway inflammation can be measured in both blood and tissue [Moore, 2010; Schleich, 2014]. Collection of sputum eosinophils must be performed at specialized centers and results can be more variable than blood eosinophils. Recent studies have also demonstrated that severe eosinophilic asthma which responds to mepolizumab can be reliably identified in a poorly controlled exacerbating phenotype by using blood eosinophil thresholds, even in the presence of high-dose ICS [Pavord, 2012; Katz, 2014].

Emerging data continues to provide further clarity on the severe asthma phenotype. In a study conducted in Amsterdam, 78 patients with severe refractory asthma and 98 with mild-to-moderate asthma were characterized with respect to their clinical, functional, and inflammatory parameters [Amelink, 2013]. As expected, patients with severe asthma consulted their treating physicians more often, made more visits to the emergency department (ED), and were more often hospitalized and admitted to the intensive care unit (ICU) than milder patients. In this study, the investigators reported a median blood eosinophil count of 250 cells/μL (140-500 cells/μL) in the severe asthma group compared with 180 cells/μL (90-310 cells/μL) in the mild-to-moderate group. More recently, data from a Belgian severe asthma registry [Schleich, 2014] of 350 severe asthma patients indicated a median blood eosinophil count of 240 cells/μL. These eosinophil counts are consistent with the counts observed in the mepolizumab severe asthma studies.

2.1.2. Severe Asthma in Children

The prevalence of severe asthma reported for the pediatric population varies widely. A study using data from the UK General Practice Research Database [Thomas, 2010] examined cases of asthma or recurrent wheezing from September 2006 through February 2007 in primary care practices. A prevalence of 1.9% (11/587) was reported for children ages <1 to 14 years classified as having severe persistent asthma based on asthma guidelines and treated with high dose ICS/LABA plus one additional controller. Another study [Solé, 2015] using the International Study of Asthma and Allergies in Childhood (ISAAC) found a 4.7% prevalence of severe asthma, defined as wheezing severe enough to limit speech in the last 12 months, in adolescents (13-14 years of age) in Brazil. Of note, these data provide estimates of severe asthma without accounting for a subset of eosinophilic asthma.

There is limited information on the pathophysiological mechanisms responsible for severe and persistent asthma, particularly in children [Fitzpatrick, 2006; Fitzpatrick, 2011]. Childhood severe asthma, often termed difficult-to-treat asthma, is associated with poor symptom control despite treatment with high doses of ICS. The clinical features that differentiate severe from mild-to-moderate asthma in children have not been well-defined [Fitzpatrick, 2006]. In an attempt to do so, a cluster analysis in children aged 6-17 years with severe asthma in the Severe Asthma Research Program (SARP) Network identified four distinct phenotypes based on 12 continuous and composite variables (Table 1) [Fitzpatrick, 2011].

Table 1 Childhood Asthma Clusters Identified in the NIH/NHLBI SARP

Cluster	Summary Description	Number of Patients	Mean Age, yrs (SD)
1	Late-onset symptomatic asthma with normal lung function	48	9 (3)
2	Early-onset atopic asthma with normal lung function	52	10 (2)
3	Early-onset atopic asthma with mild airflow limitation	32	15 (2)
4	Early-onset atopic asthma with advanced airflow limitation	29	12 (2)

However, no single phenotype corresponded well with definitions of severe asthma described in published guidelines, suggesting that severe asthma in children is highly heterogeneous. Fitzpatrick et al. described three phenotypes that were mostly atopic with varying airflow limitation and one other phenotype that was late-onset symptomatic asthma with normal lung function. Pediatric patients with more severe disease are increasingly likely to have impaired lung function, as studies have shown that despite the use of high doses of ICS and OCS, severe asthma is associated with a component of airflow obstruction that appears either non-reversible or, at best, difficult to reverse.

While the majority of histology studies characterizing asthma have been conducted in adult patients, similar pathological characteristics to adults have been noted in available studies of pediatric patients [Payne, 2001; Holgate, 2010]. A study of 28 children with difficult asthma (defined as persistent bronchial obstruction [FEV_1 <80% of predicted

values], despite high doses of ICS and regular treatment with long-acting β2-agonists), found that symptomatic children were more likely to be associated with activated eosinophils in the epithelium and a Th2-type cytokine profile in their bronchoalveolar lavage (BAL) specimen compared to children with few symptoms [de Blic, 2004]. This is also supported by a second independent report on severe asthma in children [Bossley, 2012]. Overall, these data suggest the characteristics of eosinophilic asthma in pediatric patients are less common than atopic asthma and more likely to be present in more severe patients. The evidence supports the co-existence of atopy (allergy sensitization) and eosinophilic (airway inflammation) phenotype in both pediatric patients and adults which contributes to the expression of severe uncontrolled persistent asthma.

2.2. Mechanism of Action

Eosinophilic inflammation of the airways plays a central role in the pathogenesis of asthma [Rothenberg, 1998; Wardlaw, 2000]. The frequency of asthma exacerbations appears to be closely related to airway inflammation [FitzGerald, 2006]. Eosinophilic inflammation is promoted by T-helper 2 (Th2) cytokines.

Mepolizumab binds with high specificity and affinity to human interleukin 5 (IL-5), the key Th2 cytokine responsible for regulation of blood and tissue eosinophils. The over-production of IL-5 has been specifically reported in patients with a variety of eosinophil-associated disorders including asthma [Robinson, 1992; Sur, 1995]. Th2-driven disease promotes tissue eosinophilia and therefore lung damage [Woodruff, 2009]; studies on biopsy and sputum have shown that abnormal eosinophils are key drivers of uncontrolled disease [Nair, 2009; Flood-Page, 2003]. Good correlations have been shown between elevated sputum eosinophil levels and blood eosinophil counts [Korevaar, 2015]. Mepolizumab prevents IL-5 from binding to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface and thus inhibits IL-5 signaling and the over-expression of peripheral blood and tissue eosinophils. By neutralizing IL-5 and reducing eosinophilic inflammation in the lung, mepolizumab reduces exacerbations and improves asthma control. Since mepolizumab binds only to IL-5, it is not expected to elicit unintended biological consequences which can result from off-target or non-specific binding.

Available data do not indicate that reduction of eosinophils has any untoward effects on normal health [Gleich, 2013]; patients lacking eosinophils in association with immunodeficiency or as a consequence of IgG-mediated eosinophil precursor destruction do not display any distinguishing abnormalities related to the eosinophil reduction.

Thus, a therapeutic strategy targeting IL-5 with mepolizumab represents a targeted therapeutic option which results in reduced eosinophil counts and important clinical benefits for patients with eosinophilic inflammation associated with severe asthma despite receiving optimized standard of care therapy.

As presented in this Briefing Document, mepolizumab, based on its favorable safety profile, the robust data supporting its clinically meaningful efficacy in reducing frequent and severe exacerbations, improvements in quality of life, and its utility in reducing the requirement for daily systemic corticosteroids, provides a treatment option for patients

with severe eosinophilic asthma who otherwise have no, or limited therapeutic treatment options.

2.3. Proposed Indication and Dosage

The following is a proposed indication for mepolizumab. This is submitted as a framework for discussion which includes characteristics of patients who are most likely to benefit from treatment with mepolizumab. The proposed indication is currently under discussion with the Food and Drug Administration (FDA).

> *NUCALA® is indicated for add-on maintenance treatment of severe eosinophilic asthma, as identified by blood eosinophils greater than or equal to 150 cells/µl at initiation of treatment or blood eosinophils greater than or equal to 300 cells/µl in the past 12 months, in patients aged 12 years and older. NUCALA has been shown to reduce exacerbations of asthma in patients with an exacerbation history [see Clinical Studies (14)]).*

NUCALA is not indicated for treatment of other eosinophilic conditions and or for the relief of acute bronchospasm or status asthmaticus.

Mepolizumab will be provided as a lyophilized powder for reconstitution and administration by a healthcare professional. The recommended dosage is 100 mg administered by subcutaneous (SC) injection into the upper arm, thigh, or abdomen once every 4 weeks.

2.4. Regulatory History

A pre-investigational new drug (IND) application meeting to discuss the acceptability of the pre-clinical package and planned Phase I study of mepolizumab in patients with asthma was held with the FDA on October 22, 1996. An IND was subsequently filed on December 20, 1996. Following clearance of the IND, the first clinical study began in patients with mild asthma on May 6, 1997.

Subsequent meetings between FDA and GlaxoSmithKline (GSK) to discuss the clinical development of mepolizumab for patients with asthma were held on February 24, 2006, April 21, 2009, and May 4, 2012. Key results from proof of concept Study CRT110184 were available for the April 21, 2009 meeting. Key results from exacerbation and dose-ranging Study MEA112997 were available for the May 4, 2012 meeting. Based on clinical results and scientific rationale, the focus of world-wide registration-directed, placebo-controlled trials became patients with severe asthma with evidence of eosinophilic airway inflammation who were receiving standard of care therapy. The primary endpoint was agreed as reduction in the rate of exacerbations. For purposes of clear labelling, it was acknowledged that the intended patient population must be readily identifiable in a real world setting. Blood eosinophil measurements were discussed as a practical approach, including demonstration of efficacy and safety results within and outside of the intended patient population. Results from a steroid sparing study were agreed to provide supportive evidence for efficacy.

A pre-submission meeting was held January 15, 2014 where the proposed contents of the BLA were discussed. The BLA was submitted on November 4, 2014 with a proposed indication for patients with severe asthma whose blood eosinophil levels meet pre-specified criteria practical to a prescribing physician and established in Phase III studies as associated with benefit. Safety has been well characterized within and outside of the proposed indicated patient population (i.e., milder asthma, eosinophilic esophagitis, eosinophilic granulomatosis with polyangiitis [EGPA]) during development. The 120 Day Safety Update was submitted on March 3, 2015 providing additional longer-term safety information primarily from open label extension studies that is consistent with data included in the original BLA.

3. CLINICAL DEVELOPMENT PROGRAM

3.1. Overview

The core Phase II-III clinical development program for mepolizumab in severe eosinophilic asthma was comprised of 9 studies and over 1500 patients (Figure 4). Since mepolizumab is a first in class medication, as the program progressed, key learnings emerged which provided the rationale and informed on the design for each study. Each stage of the program provided building blocks to characterize the efficacy and safety profile of patients most likely to benefit from treatment with mepolizumab (see Section 5.2).

For ease of review, study identification numbers are presented in a truncated 3-digit format (last 3 numbers) throughout this Briefing Document. Full and truncated study numbers are shown in Table 2.

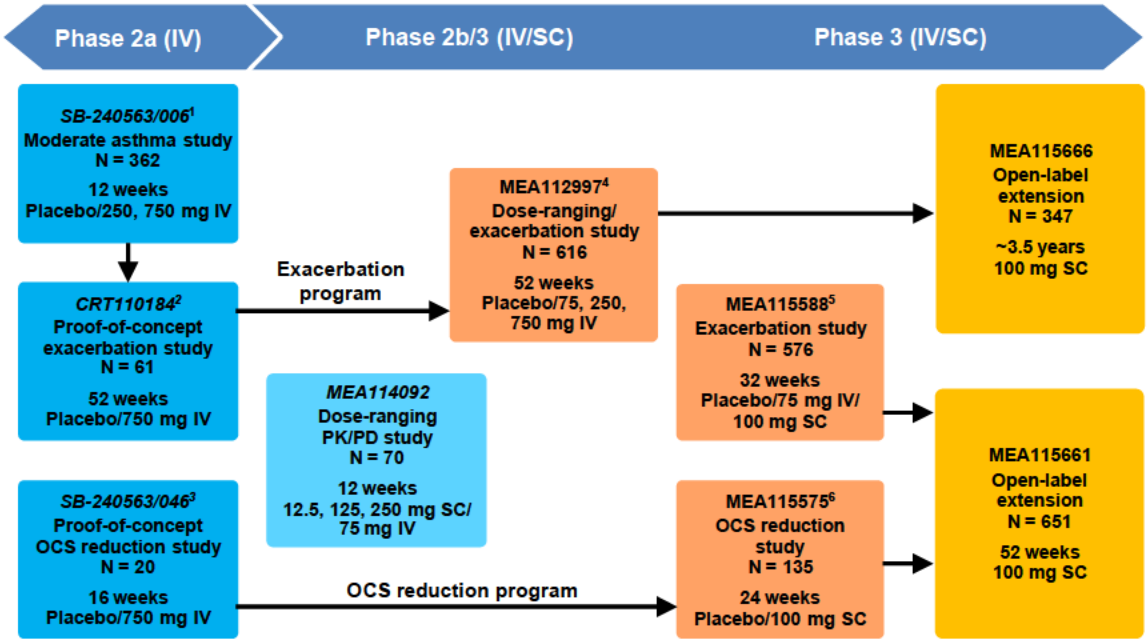
Four Phase IIa studies (briefly described in Section 3.2.1), provided information important to the development of mepolizumab in severe eosinophilic asthma:

- Moderate Asthma Study 006
- Proof-of-Concept Exacerbation Study 184 (investigator-sponsored)
- Proof-of-Concept OCS Reduction Study 046 (investigator-sponsored)
- Dose-ranging Pharmacokinetic (PK)/Pharmacodynamic (PD) Study 092

Five key studies, which are the focus of this Briefing Document, provide the primary support for the efficacy and safety of mepolizumab in severe eosinophilic asthma (described in the section indicated):

- Exacerbation Studies 997 and 588 (Section 3.2.2)
- OCS Reduction Study 575 (Section 3.2.3)
- Open-Label Extension (OLE) Studies 666 and 661 (Section 3.2.4)

Figure 4 **Clinical Development Program for Mepolizumab in Severe Eosinophilic Asthma**



1. Flood-Page, et al. Am J Respir Crit Care Med 2007;176:1062-71.
2. Haldar, et al. N Engl J Med 2009;360:973-84.
3. Nair, et al. N Engl J Med 2009;360:985-93.
4. Pavord, et al. Lancet 2012;380:651-59.
5. Ortega, et al. N Engl J Med 2014;371:1198-1207.
6. Bel, et al. N Engl J Med 2014; 371:1189-97.

Studies 006, 184, and 046 informed on the population appropriate for treatment with mepolizumab as being those patients with severe asthma who use daily high-dose ICS (with or without maintenance OCS), have presence of airway eosinophilia, and a history of exacerbations (see Section 3.2.1.1 and Section 5.2).

Patients with severe eosinophilic asthma have frequent exacerbations and a significant burden of corticosteroid use. Reduction of exacerbation was the primary endpoint for Studies 997 and 588, and reduction of steroid use was the primary endpoint for Study 575. The OLE Studies 666 and 661 provide additional long-term safety data.

Mepolizumab was initially studied using IV administration; however, the development program progressed to provide data characterizing the SC route of administration due to clear patient and healthcare provider preference for SC administration. Study 092 evaluated the PK/PD relationship following mepolizumab IV and SC in patients with asthma and elevated blood eosinophils and was used to guide dose selection. The proposed therapeutic dose for mepolizumab is 100 mg SC; 75 mg IV is the corresponding IV dose based on the absolute bioavailability with similar PD, safety, and efficacy.

3.2. Study Design

An overview of the study designs for the 9 studies in the mepolizumab severe eosinophilic asthma development program discussed in this Briefing Document is presented in Table 2. Further pertinent design information (study objective, enrollment criteria, and study endpoints) and key learnings obtained from each study are described in

the subsequent subsections. It is important to remember that mepolizumab is administered as an add-on treatment and that the placebo arm is therefore standard of care asthma therapy including high-dose ICS + long-acting $beta_2$ receptor agonist [LABA], leukotriene receptor antagonist [LTRA]or theophylline, and/or OCS.

Table 2 Study Design Overview

Study Number	Design	Treatments[1]	Number of Patients Enrolled/Completed
Phase IIa Studies			
SB-240563/006 (Study 006) 	Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter	Mepolizumab 250 mg IV Mepolizumab 750 mg IV Placebo IV One dose every 4 weeks for 12 weeks	120/110 116/112 126/119 Total: 362/341
CRT110184 (Study 184) Proof-of-concept	Randomized, Double-blind, Placebo-controlled, Parallel-group, Single-center, Investigator-sponsored	Mepolizumab 750 mg IV Placebo IV One dose every 4 weeks for 52 weeks	29/27 32/29 Total: 61/56
SB-240563/046 (Study 046) Proof-of-concept	Randomized, Double-blind, Placebo-controlled, Parallel-group, Single-center, Investigator-sponsored	Mepolizumab 750 mg IV Placebo IV One dose every 4 weeks. Duration of study up to 20 weeks and maximum of 5 doses	9/8 11/11 Total: 20/19
MEA114092 (Study 092)	Randomized, Open-label, Dose ranging, Parallel-group, Multicenter	Mepolizumab 12.5 mg SC Mepolizumab 125 mg SC Mepolizumab 250 mg SC Mepolizumab 75 mg IV One dose every 4 weeks for 12 weeks	21/20 15/14 23/21 11/11 Total: 70/66
Exacerbation Studies			
MEA112997 (Study 997)	Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter	Mepolizumab 75 mg IV Mepolizumab 250 mg IV Mepolizumab 750 mg IV Placebo IV One dose every 4 weeks for 52 weeks	153/129 152/131 156/133 155/127 Total: 616/520
MEA115588[2] (Study 588)	Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter	Mepolizumab 75 mg IV + Placebo SC Mepolizumab 100 mg SC + Placebo IV Placebo IV + Placebo SC One dose every 4 weeks for 32 weeks	191/175 194/185 191/179 Total: 576/539 525 continued in Study MEA115661
OCS Reduction Study			
MEA115575[2] (Study 575)	Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter	Mepolizumab 100 mg SC Placebo SC One dose every 4 weeks for 24 weeks	69/66 66/62 Total: 135/128 126 continued in Study MEA115661
Open-label Extension Studies			
MEA115666 (Study 666)	Open-label, Multicenter	Mepolizumab 100 mg SC One dose every 4 weeks for ~3.5 years	347/0 (ongoing)
MEA115661[2] (Study 661)	Open-label, Multicenter	Mepolizumab 100 mg SC One dose every 4 weeks for 52 weeks	651/585 (concluded)[3] 337 continued in Study 201312

1. Placebo = normal saline; maintenance asthma therapy continued throughout the study in all treatment arms
2. Eligible patients who completed the study could continue treatment in an open-label extension study
3. All patients have attended their last study visit; analysis and reporting have not been completed yet

3.2.1. Phase IIa Studies

3.2.1.1. Moderate Asthma Study 006

Primary Objective: To evaluate the safety and efficacy of mepolizumab 250 and 750 mg IV, compared with placebo, administered once a month on three occasions (12-week treatment period) in patients with asthma.

Enrollment Criteria: Patients 18 to 55 years of age with a diagnosis of asthma, as defined by the GINA guidelines, for at least 12 months were eligible. Additional inclusion criteria were pre-bronchodilator FEV_1 between ≥50% and ≤80% of predicted normal, FEV_1 reversibility ≥12%, and current treatment with medium doses of ICS (400 to ≤1000 mcg beclomethasone dipropionate [BDP] or 200 to ≤500 mcg fluticasone propionate [FP], or equivalent).

Efficacy Endpoints: The primary efficacy endpoint was change from baseline in morning daily peak expiratory flow (PEF) (mean of the measures recorded in the 7 days preceding the Week 12 Visit). Secondary efficacy endpoints were change from baseline in FEV_1, total asthma symptom scores, use of rescue medication, and eosinophil count in blood and sputum. Asthma exacerbation rate was a tertiary efficacy variable.

Safety Endpoints: Adverse events (AEs), laboratory data, electrocardiograms (ECGs), and vital signs.

Key Learnings: The results of this early study [Flood-Page, 2007] showed mepolizumab provided limited clinical benefit on pulmonary function endpoints and symptoms (no consistent changes from baseline in morning PEF, clinic FEV_1 or asthma summary symptom score between the placebo group and the mepolizumab 250 mg and 750 mg IV groups at Week 12, at endpoint, or at follow-up Week 20) in patients with moderate asthma. However, among the relatively small number of exacerbations recorded, the number of patients experiencing exacerbations over Weeks 0-20 was noted to be lower in the 750 mg IV group (11 patients, 10%) compared with placebo (20 patients, 16%). Results of this study contributed to the understanding that mepolizumab should be targeted to a more severe population experiencing frequent exacerbations and evidence of eosinophilic inflammation. No safety concerns were identified.

3.2.1.2. Proof-of-Concept Exacerbation Study 184

Primary Objective: To study the effect of 52 weeks of mepolizumab 750 mg IV treatment on the frequency of exacerbations among patients who had severe asthma and evidence of eosinophilic airway inflammation despite treatment with high doses of corticosteroids (ICS with or without OCS).

Enrollment criteria: Patients >18 years of age with a diagnosis of severe asthma according to ATS criteria [ATS, 2000], sputum eosinophils >3% on at least one occasion in the previous 2 years despite high-dose corticosteroid treatment, and at least two exacerbations requiring rescue prednisolone treatment in the previous 12 months.

Efficacy Endpoints: The primary outcome measure of the study was the frequency of severe exacerbations of asthma. Key secondary outcome measures were, post-bronchodilator percent predicted FEV_1, airway hyper-responsiveness, Asthma Quality of Life Questionnaire (AQLQ) score, symptom scores, and changes in eosinophil counts in blood and sputum.

Safety Endpoints: AEs, laboratory tests, physical examinations, and vital sign measurements. SAE data were reported to GSK.

Key Learnings: Exacerbations can be reduced (43% reduction [p=0.02] compared with placebo) with mepolizumab when patients are selected based on a marker of lung eosinophilia [Haldar, 2009]. The findings from this study informed on protocol development for Study 997 (see Section 3.2.2.1). There were no safety concerns attributable to mepolizumab.

3.2.1.3. Proof-of-Concept OCS Reduction Study 046

Objective: The primary objective of the study was to examine the prednisone-sparing effect of mepolizumab 750 mg IV in patients ≥18 years with severe asthma and persistent sputum eosinophilia (≥3%). This study had three phases: Phase 1 evaluated the effect of one infusion of study drug at 4 weeks; Phase 2 evaluated the reduction in the dose of prednisone after two infusions of study drug; and Phase 3 was a washout phase where patients were followed for 8 weeks after the last infusion of a study drug.

Enrollment Criteria: Patients with asthma who required treatment with high doses of ICS and oral prednisone to control symptoms and still had persistent sputum eosinophilia.

Efficacy Endpoints: The primary outcomes of the study were the proportion of patients with exacerbations in each study group and the mean reduction in the dose of prednisone as a percentage of the maximum possible reduction, according to the protocol used in Phase 2 of the study. Other variables measured were AQLQ score, FEV_1, and quantitative counts of sputum and blood eosinophils.

Safety Endpoints: AEs were monitored and laboratory tests were performed. SAE data were reported to GSK.

Key Learnings: OCS can be reduced with mepolizumab when OCS-dependent patients are selected based on induced sputum evidence of lung eosinophilia (84% reduction in daily prednisone dose with mepolizumab compared to 48% with placebo) [Nair, 2009]. The findings from this study informed on protocol development for Study 575 (see Section 3.2.3). Of note, fewer patients treated with mepolizumab (1/9 patients, 11%) experienced asthma exacerbations compared with placebo (10/11 patients, 91%) (p=0.008) further supporting reduction of exacerbations in a severe eosinophilic population. There were no safety concerns attributable to mepolizumab.

3.2.1.4. Dose-Ranging PK/PD Study 092

Objective: The primary objective of the study was to demonstrate that the pharmacokinetic (PK)/ pharmacodynamics (PD) relationship between the exposure of

subcutaneously (SC) administered mepolizumab (12.5, 125, and 250 mg) and a marker of response, blood eosinophil, is comparable to that observed following IV administration. Inclusion of the 75 mg IV dose enabled assessment of the absolute bioavailability of the SC route. This study was conducted to further support the dosing strategy and route of administration.

Enrollment Criteria: Patients with asthma aged 18 to 65 years having been on a stable dose of their current asthma medications for 12 weeks prior to screening. Patients had an FEV_1 of ≥45% and <90 % of predicted normal value and evidence of airway reversibility or airway hyper-responsiveness. Patients had documented evidence of blood eosinophilia within 12 months of screening (≥300 cells/μL) and evidence of blood eosinophilia at screening (≥300 cells/μL; 4 out of 70 patients had ≥200 cells/μL).

PK/PD Endpoints:

- Change from baseline in blood eosinophil counts as assessed by the exposure-response relationship
- Area under the plasma concentration-time curve (AUC), maximum plasma concentration (Cmax), time to Cmax (Tmax) and terminal half-life (t½) of mepolizumab

Safety Endpoints: AEs, vital signs, ECGs, and clinical laboratory values. ADA levels were measured.

Key Learnings: This study characterized the pharmacological dose response to mepolizumab and identified 100 mg SC (and the comparable IV dose of 75 mg) as the dose providing 90% of the maximal achievable pharmacological response measured by the reduction in blood eosinophils (see Section 4.2); this dose was carried forward to the Phase III studies. Mepolizumab was generally well tolerated; the percentages of patients reporting AEs after SC and IV dosing were similar (56% vs. 55%). There were no safety concerns attributable to mepolizumab.

3.2.2. Exacerbation Studies

3.2.2.1. Study 997

Objective: To evaluate the efficacy and safety of mepolizumab 75, 250, and 750 mg IV compared with placebo over a 52-week treatment period in adult and adolescent patients with severe eosinophilic asthma.

Enrollment criteria: Patients with severe asthma, aged ≥12 years with a requirement for regular treatment with high dose ICS (≥880 mcg/day [ex-actuator] FP or equivalent) with or without maintenance OCS, in the previous 12 months. Patients were also required to have need for additional controller medication (e.g., LABA, LTRA, or theophylline) and evidence to support eosinophilic airways disease. Eosinophilic airway inflammation could be demonstrated at screening, or documented in the previous 12 months, by one of the following characteristics:

- Sputum eosinophils ≥3% ***or***
- An elevated peripheral blood eosinophil level of ≥300 cells/μL ***or***
- Exhaled nitric oxide (FeNO) ≥50 ppb [Dweik, 2011] ***or***
- Prompt deterioration of asthma control (based on documented clinical history or objective measures) following a ≤25% reduction in regular maintenance dose of inhaled or oral corticosteroid dose in the previous 12 months.

Patients further were required to have a pre-bronchodilator FEV_1 <80% predicted and a history of two or more asthma exacerbations requiring treatment with systemic corticosteroids in the 12 months prior to Visit 1, despite the use of high-dose ICS.

Efficacy Endpoints: The primary endpoint was frequency of exacerbations of asthma (defined in Section 3.3.1.1). Other key endpoints were frequency of exacerbations requiring hospitalization (including intubation and admittance to an ICU) and/or ED visit, frequency of exacerbations requiring hospitalization only, mean change from baseline in clinic pre-and post-bronchodilator FEV_1, AM PEF, Asthma Control Questionnaire (ACQ-6) score, AQLQ score, and clinician- and patient-rated overall evaluation of response to therapy.

Safety Endpoints: AEs, clinical laboratory tests, vital signs, and 12-lead ECGs. Blood samples were obtained for immunogenicity, pharmacokinetic, and pharmacodynamic assessments.

Key Learnings: All three doses of mepolizumab were shown to be similarly effective in reducing exacerbations [Pavord, 2012], thus the lowest dose of 75 mg IV was carried forward to the subsequent Phase III study. Further, the data from this study was modeled to identify which baseline characteristics best predicted response to mepolizumab; this ultimately defined the blood eosinophil thresholds (biomarker) for implementation into the development program (see Section 5.2). Efficacy and safety results are presented in Section 4.3 and Section 6, respectively.

3.2.2.2. Study 588

Objective: The primary objective of this study was to evaluate the efficacy of mepolizumab versus placebo on the frequency of exacerbations in patients ≥12 years with severe uncontrolled asthma and evidence of eosinophilic inflammation. This study examined IV and SC administration of mepolizumab using doses based on results of Study 997 (75 mg IV) and Study 092 (100 mg SC).

Enrollment Criteria: The inclusion criteria were the same as Study 997, except eosinophilic airway inflammation had to be documented by one of the following:

- An elevated peripheral blood eosinophil count of ≥300/μL demonstrated in the past 12 months prior to Screening ***or***
- An elevated peripheral blood eosinophil count of ≥150/μL at baseline.

Efficacy Endpoints: The primary efficacy endpoint was the frequency of exacerbations of asthma (defined in Section 3.3.1.1). Other key efficacy endpoints were: frequency of exacerbations requiring hospitalization (including intubation and admittance to an ICU) and/or ED visits; frequency of exacerbations requiring hospitalization only, mean change from baseline in clinic pre-and post-bronchodilator FEV_1; AM PEF, St. George's Respiratory Questionnaire (SGRQ), and ACQ-5 score, and clinician- and patient-rated overall response to therapy.

Safety Endpoints: AEs, including systemic (i.e., allergic/IgE-mediated and non-allergic) and injection site reactions, clinical laboratory parameters, vital signs; assessment of immunogenicity, and 12-lead ECGs.

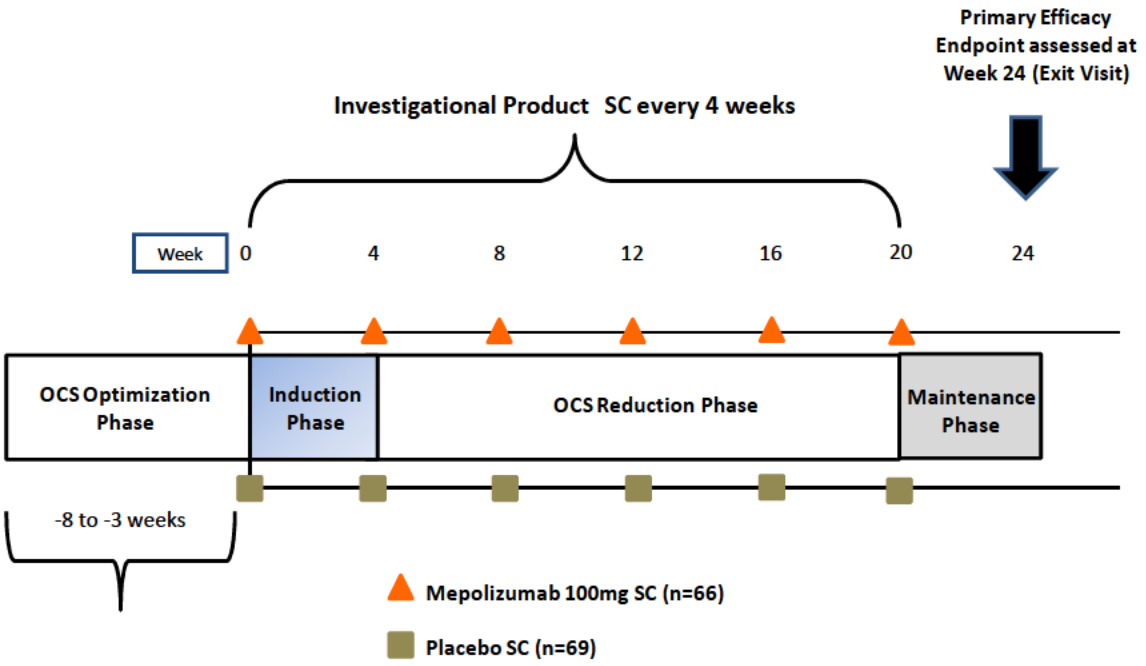
Key Learnings: This study demonstrated clinical comparability of the 75 mg IV and 100 mg SC dosing regimens, reconfirmed the exacerbation reduction effects shown in Study 997 using predefined eosinophil thresholds, and showed definitive improvements in lung function, asthma control, and quality of life [Ortega, 2014]. Efficacy and safety results are presented in Section 4.3 and Section 6, respectively.

3.2.3. OCS Reduction Study 575

Primary Objective: To compare the effects of 100 mg SC mepolizumab add-on therapy with placebo on reducing the use of maintenance OCS in systemic corticosteroid-dependent patients with severe asthma with elevated eosinophils.

Additional Study Design Information: This study had four phases: 1) OCS Optimization, 2) Induction, 3) OCS Reduction, and 4) Maintenance (Figure 5).

Figure 5 Study 575 Phases



The OCS Optimization Phase was a run-in phase intended to assure that patients entered the double-blind treatment phase on the lowest dose of prednisone that would maintain asthma control. Patient's asthma status was assessed weekly; the lowest effective prednisone dose was defined as the dose the patient was taking prior to the emergence of asthma symptoms or the occurrence of an exacerbation. The Induction Phase was designed to allow for sufficient time for those patients randomized to the mepolizumab arm to achieve a decrease in eosinophilic inflammation prior to the reduction in prednisone. During the OCS Reduction Phase, patients received four additional doses of double-blind study treatment. Patients were assessed for prednisone reduction every 4 weeks. Prednisone dose titrations in the Optimization and Reduction phases followed pre-specified algorithms (see Appendix 9.1). Patients were maintained during the last 4 weeks of the study without any further prednisone dose adjustment (i.e., Maintenance Phase).

Enrollment Criteria: Patients ≥12 years of age with severe eosinophilic asthma, a pre-bronchodilator FEV_1 <80% predicted, and a documented requirement for regular treatment with maintenance systemic corticosteroids (5.0 to 35 mg/day prednisone or equivalent) and high-dose ICS (≥880 mcg/day [ex-actuator] FP or equivalent) were eligible. At the end of the run-in period, patients were eligible to be randomized if they had achieved a stable dose of OCS during the Optimization Phase and had an eosinophilic phenotype characterized by peripheral baseline eosinophil level ≥150 cells/μL, *or* blood eosinophil level of ≥300 cells/μL within the previous 12 months while receiving high-dose ICS plus at least one other controller medication.

Efficacy Endpoints: The primary efficacy endpoint was percent reduction of OCS dose during Weeks 20-24 compared with the baseline dose, while maintaining asthma control, categorized as follows: a) 90% to 100%, b) 75% to <90%, c) 50% to <75%, d) >0% to <50%, or e) no decrease in OCS, lack of control during Weeks 20-24, or withdrawal from treatment.

Secondary OCS endpoints during Weeks 20-24, while maintaining asthma control, included: Proportion of patients who achieved a: 1) reduction of ≥50% in their daily OCS dose, compared with baseline dose, 2) reduction of OCS dose to ≤5.0 mg, and 3) total reduction of OCS dose; and median percentage reduction from baseline in daily OCS dose.

Other key efficacy endpoints included:

- Rate of exacerbations, exacerbations requiring hospitalization and/or ED visits, and exacerbations requiring hospitalization only.
- Mean change from baseline in clinic pre-and post-bronchodilator FEV_1, AM PEF, ACQ-5 score, and SGRQ score

Safety Endpoints: AEs, including both systemic (i.e., allergic/IgE-mediated and non-allergic) and local site reactions, clinical laboratory tests, including assessment of immunogenicity, vital signs, and 12-lead ECGs.

Key Learnings: This study confirmed the ability to reduce the use of OCS in patients receiving mepolizumab while maintaining asthma control and further confirmed the clinical efficacy of the 100 mg SC dose in the refined target population [Bel, 2014]. Improvements in quality of life measured by the SGRQ were robust and consistent with Exacerbation Study 588. Efficacy and safety results are presented in Section 4.4 and Section 6, respectively.

3.2.4. Open-label Extension Studies

The primary objective of the OLE studies 666 and 661 is to further describe the long-term safety profile of mepolizumab 100 mg SC.

Safety assessments include AEs (including both systemic [i.e., allergic/immunoglobulin-E (IgE)] and local site reactions), ADA antibodies, 12-lead ECG parameters, vital signs, and clinical laboratory tests. The frequency of exacerbations, ACQ-5 score, and clinic FEV_1 are also collected.

Interim analyses of these studies as of February 28, 2014 were provided in the BLA. An updated safety analysis as of October 27, 2014 was provided in the 120 Day Safety Update. Interim efficacy and safety results from these studies are provided in Section 4.5 and Section 6, respectively.

3.2.4.1. Study 666

Study 666 includes patients who had participated in Study 997 although there was at least a 12-month treatment break between the end of the double-blind study and the start of the open-label study. This study examines the effects of mepolizumab following cessation and re-start of treatment. Patients will receive treatment for up to 3.5 years. This study is currently ongoing.

3.2.4.2. Study 661

Study 661 included patients rolled over directly from either Study 588 or Study 575. For patients entering Study 661 who had been on active treatment, there was no interruption of treatment with mepolizumab, while for patients previously receiving placebo, open-label treatment with SC mepolizumab was initiated. The study duration is 52 weeks. At the end of the study, patients with a history of life-threatening or seriously debilitating asthma and a history of improved disease control while receiving mepolizumab will be eligible for extended open-label treatment if they meet the inclusion and exclusion criteria of Study 201312. At the time of writing this Briefing Document, Study 661 has concluded (all patients have attended their last study visit; analysis and reporting have not been completed yet).

3.3. Key Clinical Trial Design Elements

3.3.1. Efficacy and Quality of Life Endpoints

Efficacy and quality of life endpoints for the three key double-blind, placebo-controlled studies are shown in Table 3.

Table 3 Key Efficacy and Quality of Life Endpoints (Exacerbation Studies 997 and 588 and OCS Reduction Study 575)

Endpoint	Study 997	Study 588	Study 575
Exacerbation Rate			
Exacerbations	✓[1]	✓[1]	✓
Exacerbations requiring emergency department visit *and/or* hospitalization	✓	✓	✓
Exacerbations requiring hospitalization	✓	✓	✓
OCS Reduction			✓[1]
Lung Function			
FEV_1	✓	✓	✓
PEF	✓	✓	✓
Asthma Control			
ACQ-6	✓		
ACQ-5		✓	✓
Quality of Life			
AQLQ	✓		
SGRQ		✓	✓
Response to Therapy Assessment	✓	✓	✓

1. Primary efficacy endpoint

Statistical analyses conducted for these endpoints are summarized in Appendix 9.2.

3.3.1.1. Asthma Exacerbations

The primary efficacy endpoint in Studies 997 and 588 was the rate of exacerbations. Exacerbations were defined as worsening of asthma, which in the investigator's opinion, required use of oral/systemic corticosteroids and/or hospitalization and/or ED visits. Exacerbations recorded by the investigator were verified to confirm that the exacerbation was associated with changes in PEF, rescue medication use, nocturnal awakening due to asthma symptoms requiring rescue medication use, or symptoms. The rate of exacerbations requiring ED visit and/or hospitalization was identified as a key secondary endpoint in Studies 997 and 588. Exacerbations requiring hospitalization alone were also analyzed separately.

3.3.1.2. Lung Function

Lung function (FEV_1) was measured pre- and post-bronchodilator (albuterol) via spirometry during clinic visits. Morning peak expiratory flow (AM PEF) was recorded daily in an electronic diary (e-Diary) over the course of the study.

3.3.1.3. Asthma Control

The effect of mepolizumab on control of asthma symptoms was measured by the Asthma Control Questionnaire (ACQ-6 in Study 997 and ACQ-5 in studies 588 and 575) [Juniper, 2005]. The questionnaire was incorporated into the patient's e-Diary and inquired about the frequency and/or severity of symptoms (nocturnal awakening, activity limitation, shortness of breath, and wheeze) and use of short-acting bronchodilator (ACQ-6 only) over the previous week. The response options for these questions were

ranked on a 7-point scale from 0 (no impairment/limitation) to 6 (total impairment/ limitation). The total score was a mean of the values recorded for the individual questions. An improvement in asthma control is indicated by a decrease in score; the commonly accepted minimal clinically important difference (MCID) is -0.5 [Juniper, 2005]. Accepted cut-points for this questionnaire are ≤0.75 indicating well-controlled asthma and ≥1.50 indicating not well-controlled asthma [Juniper, 2006]. The transition from ACQ-6 used in Study 997 to ACQ-5 in the subsequent Phase III studies simplified instrument administration by shifting the instrument focus to asthma symptoms and no longer requiring inclusion of rescue medication use. Furthermore at that time, Korn and colleagues [Korn, 2011] reported the performance of the ACQ-7 and ACQ-5 in correctly predicting GINA-defined uncontrolled asthma in patients with severe asthma. Overall, ACQ-5 proved to be superior to ACQ-7, despite the additional information about the patients' lung function and need for reliever medication that is part of the ACQ-7 score. To enable comparison of the data across studies, questions regarding symptoms were used to calculate an ACQ-5 (symptom score) for Study 997 and these results are presented in this document.

3.3.1.4. Health-related Quality of Life Instruments

For quality of life measures, the Asthma Quality of Life Questionnaire (AQLQ) was used in Study 997, but was replaced by the St. George's Respiratory Questionnaire (SGRQ) in studies 588 and 575.

The AQLQ is a self-administered questionnaire developed to evaluate the impact of asthma treatments on the quality of life of asthma sufferers [Juniper, 1993]. The AQLQ contains 32 items in four domains: symptoms, activity limitation, emotional function, and environmental stimuli. The response format consists of a 7-point scale ranging from 1 to 7 where 1 indicates total impairment and 7 indicates no impairment. The 32 items of the questionnaire are averaged to produce one overall quality of life score. Assuming a statistically significant result ($p<0.05$), the MCID in overall quality of life, or in quality of life for any of the individual domains, is a change of 0.5 points [Juniper, 1994].

The SGRQ is a well-established self-administered instrument designed to measure quality of life in patients with diseases of airway obstruction [Jones, 1992]. The SGRQ has been validated in patients with chronic airflow limitation, including both asthma and chronic obstructive pulmonary disease (COPD), and validity has been established across a range of respiratory diseases and severities [Jones, 1991]. The questionnaire consists of 50 items across three domains: impact on daily life, activity, and symptoms. The questionnaire is scored on a scale of 0-100 where higher scores indicate more limitations. The MCID of a 4-point reduction has been established for both asthma and COPD, again supporting the SGRQ as responsive to changes in disease activity in asthma [Jones, 1994; Jones, 2002].

When comparing the AQLQ with the SGRQ, there are differences in the content of the questionnaires; these differences may impact the face validity (meaning that the questionnaire "looks" appropriate to the targeted population intended to sample) and responsiveness across different asthma phenotypes. Table 4 shows the contribution of each domain to the total score of each instrument, weighted by percent. Within each domain, there are also differences in the item content. The AQLQ primarily evaluates

symptoms and symptom triggers while the SGRQ has more content evaluating attacks of breathlessness and other symptoms. The intensity of activity explored in the Activity domains of the two measures also differs. The AQLQ includes moderate and strenuous activity while the SGRQ includes a wide range of activity level providing less potential for floor and ceiling impacts. The SGRQ also includes items assessing functional limitations and impact on daily life associated with lung disease. The SGRQ has greater face validity with regard to aspects of asthma important to patients with severe asthma and frequent exacerbations (e.g., overall experience of impairment and functional limitations due to lung disease and less emphasis on symptom triggers and impacts of specific symptoms) compared with the AQLQ.

Table 4 AQLQ vs. SGRQ

	AQLQ		SGRQ	
Domains	**Symptoms**	**37.5%**	**Impact on daily life**	**53.1%**
	Activity limitation	34.4%	Activity	30.3%
	Emotional function	15.6%	Symptoms	16.6%
	Environmental stimuli	12.5%		

Adapted from Juniper, 1992 and Jones, 1991

The AQLQ has been shown to be responsive in patients with severe allergic asthma [Brusselle, 2009; Chipps 2006] but not consistently responsive in other populations of patients with severe asthma [Castro, 2010; Brusselle, 2013; Kjerstjens, 2012].

In contrast, the SGRQ has recently been shown by independent investigators to be effective in measuring health status of patients with severe asthma. In a cohort of severe asthma patients, the SGRQ discriminated between patients with frequent exacerbations (≥2) compared to those with few (<2) exacerbations [Kupczek, 2013]. In addition, in a study of patients with severe, uncontrolled asthma in Brazil [Carvalho-Pinto, 2012], the SGRQ total and domain scores were strongly correlated with both the ACQ and Asthma Control Test (ACT). Overall, evidence supports the SGRQ as having content validity, construct validity, and responsiveness in patients with severe asthma. Based on the utility of this tool in patients with severe asthma, the SGRQ was introduced as the quality of life instrument for the Phase III studies 588 and 575.

3.3.1.5. Response to Therapy Assessment

Overall response to therapy was assessed separately by the investigator and the patient using a 7-point rating scale ranging from 1 (significant improvement) to 7 (significant worsening). The recall period was the previous 2 months.

3.3.2. OCS Reduction Study

Patients with severe asthma treated with maintenance OCS are at risk of AEs associated with systemic corticosteroid use. The proof-of-concept Study 046 [Nair, 2009] demonstrated that mepolizumab was effective in reducing the dose of prednisone while preventing exacerbations, decreasing blood and sputum eosinophil numbers, and improving lung function and quality of life (see Section 3.2.1.3). Following on the

positive results in this proof-of-concept study along with the identification of a mepolizumab responder population, a Phase III study (575) was conducted in patients who had a peripheral blood eosinophil count of ≥150/μL at baseline *or* ≥300/μL in the 12 months prior screening despite being maintained on high-dose ICS and OCS.

Oral steroid reduction studies are difficult to design and analyze because many patients are not on optimal doses of OCS (on higher or lower doses than required) and there is also a potential for a strong placebo effect. In Study 575, an OCS optimization phase was incorporated prior to double-blind treatment (see Section 3.2.3) to establish that patients genuinely needed OCS for control of their asthma and the dose required. This design feature likely accounts for the lower placebo effect seen in this study compared with Study 046 and other OCS reduction studies [Davies, 2000; Evans, 2001; Lock 1996; Nizankowska, 1995; Shiner, 1990]. Before initiating OCS reductions, patients were required to be stable at their optimized dose during the last 2 weeks prior randomization (optimization phase) plus 4 additional weeks during the induction phase, for a total of 6 weeks. OCS reduction during the blinded study period was only allowed if asthma control was documented using the ACQ-5 and, in the investigator's judgment, a reduction was appropriate. As such, poor asthma outcomes in the placebo group should not have been an artifact of spurious OCS reduction. In fact, both FEV_1 and ACQ-5 results showed that lung function and asthma control were well-maintained over the course of the study (see Section 4.4).

4. EFFICACY RESULTS

The efficacy discussion is focused on the results for mepolizumab 100 mg SC, the dose proposed for marketing, and the 75 mg IV dose which provides comparable systemic exposure. Results for higher doses are shown for completeness. It is noteworthy that the efficacy and safety profile of higher doses does not alter the benefit/risk profile of mepolizumab.

4.1. Overview

Key Findings:

Mepolizumab 100 mg SC every 4 weeks is the target therapeutic dose and route of administration for registration in patients with severe eosinophilic asthma; mepolizumab 75 mg IV every 4 weeks is the corresponding IV dose based on the absolute bioavailability with similar PD and efficacy.

The randomized, multi-center, placebo-controlled Exacerbation Studies (997 and 588) and OCS Reduction Study (575) demonstrate the efficacy of mepolizumab and support the use of mepolizumab 100 mg SC every 4 weeks as an add-on therapy for the treatment of patients with severe eosinophilic asthma.

Treatment with mepolizumab 100 mg SC or 75 mg IV compared with placebo in patients currently receiving standard of care therapy in the Exacerbation Studies:

- Reduced the rate of exacerbations by approximately 50%. These results were

replicated in Studies 997 and 588.

- Reduced the rate of exacerbations requiring hospitalizations and/or ED visits by 32% to 61% and the rate of exacerbations requiring hospitalization alone by 35% to 63%.
- The efficacy of mepolizumab in exacerbation reduction was maintained with no evidence of loss of effect over 32 and 52 weeks of treatment with 100 mg SC and 75 mg IV, respectively.
- Improved lung function (FEV_1), asthma control (ACQ-5), and quality of life (SGRQ and clinician and patient-rated overall response to therapy) in the target population. In Study 588, the mean improvements in SGRQ total score exceeded the MCID for the instrument.
- Study 997 established the use of a blood biomarker to identify the target population which was confirmed in Study 588. In both studies, mepolizumab produced consistent reductions in blood eosinophil counts which were sustained for the duration of treatment.

In Study 575, OCS-dependent patients treated with mepolizumab 100 mg SC plus standard of care achieved greater reductions in prednisone dose while maintaining or improving asthma control compared with placebo plus standard of care. At the end of the treatment period, the median daily dose of prednisone was reduced from 10 mg to 3.1 mg in the mepolizumab group, but only from 12.5 mg to 10 mg in the placebo group. This study confirmed the finding of the Proof-of-Concept Study 046 and provides further evidence for the OCS reducing effect of mepolizumab. Patients treated with mepolizumab also showed statistically significant and/or clinically relevant reduction in exacerbations, improvements in quality of life (mean SGRQ total score exceeded the MCID), asthma control, and lung function.

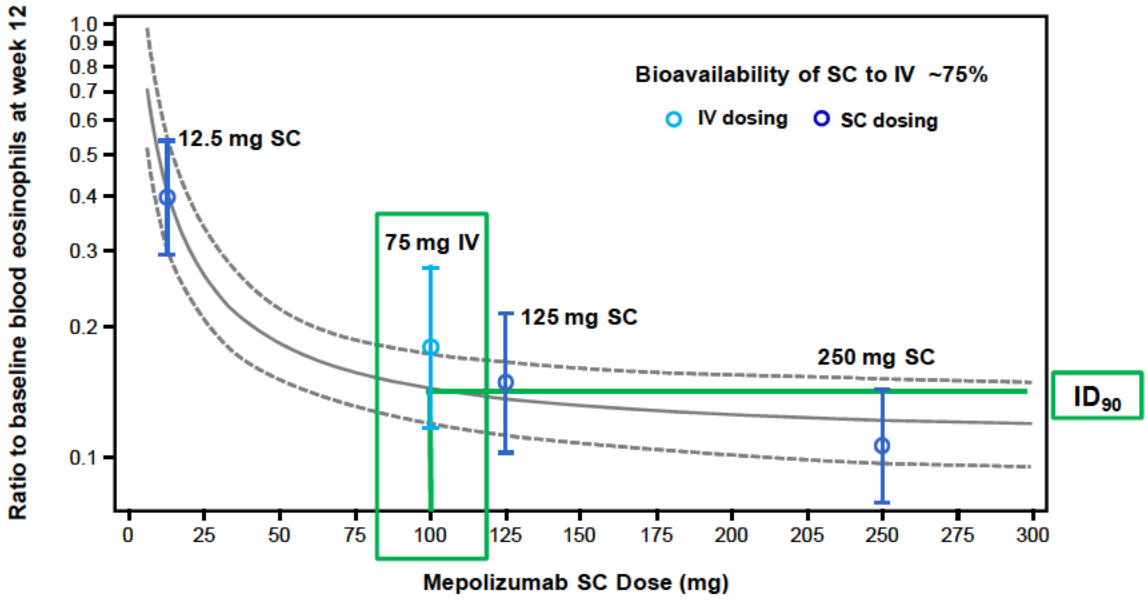
4.2. Dose and Regimen Selection

The proposed dose of mepolizumab is 100 mg SC every 4 weeks. This dose corresponds to the lowest IV dose investigated in the dose-ranging Study 997 that provided maximum clinical efficacy (reduction of exacerbations). This dose also provides 90% of the maximum achievable reduction in blood eosinophils which is the pharmacologic goal of mepolizumab. The 4-weekly dosing interval is supported by the half-life of mepolizumab (20 days [Smith, 2011]) providing approximately two-fold drug accumulation at steady-state along with consistent maintenance of pharmacological effect over this period. Further information is provided in Appendix 9.3.

Study 092 characterized the pharmacological dose-response relationship for blood eosinophil reduction and showed that the route of administration did not affect the mepolizumab eosinophil concentration-response relationship. Three SC doses of mepolizumab (12.5, 125, and 250 mg) and a 75 mg IV dose were examined in patients with asthma with evidence of blood eosinophilia. This study identified 100 mg SC (or equivalently 75 mg IV) as the dose providing 90% of maximum achievable eosinophil response (Figure 6). The 12.5 mg SC dose showed limited effect with less inhibition of

blood eosinophils compared with the other doses. In a previous study in healthy volunteers [Ortega, 2014], the absolute bioavailability of SC mepolizumab was determined to be approximately 75% compared with IV dosing; this result was confirmed in this study. Thus, a 100 mg SC dose, which provides comparable exposure to a 75 mg IV dose, was selected as the corresponding SC dose for Phase III studies following Study 997.

Figure 6 **Dose Response Ratio Compared to Baseline in Blood Eosinophils (Geometric Mean +/- Standard Error) In Adult Asthmatic Patients with Elevated Blood Eosinophils (Study 092)**



The selection of this dose was supported by Study 588 which replicated the efficacy of the 75 mg IV dose seen in Study 997 (47% and 48% reductions in exacerbations in Studies 997 and 588, respectively) and showed that 100 mg SC was comparable (53% reduction in exacerbations) (see Section 4.3.3).

4.3. Exacerbation Studies 997 and 588

4.3.1. Demographics and Baseline Characteristics

4.3.1.1. Demographics

The demographics and baseline characteristics of patients recruited for Studies 997 and 588 were similar and there were no notable differences between the treatment groups within each study. The population was representative of patients with severe eosinophilic asthma.

The majority of patients were female (60%), the mean age was approximately 50 years (2% adolescent, 9% elderly ≥65 years), and patients tended to have an elevated body mass index (28 kg/m^2) (Table 5). The majority of patients (84%) were White. Although

patients of African descent comprised 3% of the global Intent-to-Treat (ITT) Population, of the patients enrolled at US sites, 25% were African-American.

The proportion of adolescent patients enrolled in the severe eosinophilic asthma studies was small. Evidence supports the co-existence of atopy (allergy sensitization) and an eosinophilic (airway inflammation) phenotype in pediatric/adolescent patients; however, the eosinophilic-driven phenotype is less prevalent in children [Fitzpatrick, 2011; Jenkins, 2003].

Table 5 Demographics (Studies 997 and 588, ITT Population)

Demographic	Study 997 N=616	Study 588 N=576	Total N=1192
Gender, n (%)			
Female	387 (63)	328 (57)	715 (60)
Male	229 (37)	248 (43)	477 (40)
Age, yr			
Mean (SD)	48.6 (11.28)	50.1 (14.28)	49.3 (12.83)
Min, Max	15, 74	12, 82	
Age Group, n (%)			
12-17 years	1 (<1)	25 (4)	26 (2)
18-64 years	590 (96)	471 (82)	1061 (89)
≥65 years	25 (4)	80 (14)	105 (9)
Race, n (%)			
White	554 (90)	450 (78)	1004 (84)
Asian	35 (6)	106 (18)	141 (12)
African American/African Heritage	23 (4)	16 (3)	39 (3)
American Indian or Alaskan Native	2 (<1)	1 (<1)	3 (<1)
Other (Mixed Race)	2 (<1)	3 (<1)	5 (<1)
US Patients, n	78	67	145
African American, n (%)	22 (28)	14 (21)	36 (25)
Ethnicity, n (%)			
Not Hispanic/Latino	554 (90)	525 (91)	1079 (91)
Hispanic/Latino	62 (10)	51 (9)	113 (9)
Body Mass Index, kg/m²			
Mean (SD)	28.47 (5.950)	27.77 (5.830)	28.13 (5.900)
Min, Max	17.4, 52.2	16.1, 49.7	16.1, 52.2

4.3.1.2. Baseline Characteristics

Patients enrolled in the Exacerbation Studies had long duration of asthma with a mean of at least 19 years; half of the patients were atopic (Table 6). The mean baseline blood eosinophils were 250 and 290 cells/μL. Despite being treated with high dose ICS plus an additional controller medication (and 27% with daily OCS), patients had a history of frequent exacerbations with a mean of 3.6 per year. Over one third of the patients (39%) required an ED visit or hospitalization due to an exacerbation in the previous year. The mean percent predicted FEV_1 was approximately 60% and FEV_1/FVC ratio was low (~0.65), which is consistent with severe disease [Chung, 2014]. The baseline ACQ

scores (2.2 and 2.4) were greater than the threshold of 1.5 for defining uncontrolled disease.

Table 6 Asthma History (Studies 997 and 588, ITT Population)

Asthma History	Study 997 N=616	Study 588 N=576
Duration of Asthma, yr		
Mean (SD)	19.1 (14.3)	19.9 (13.8)
Duration of Asthma Category, n (%)		
≥1 to <5 years	79 (13)	60 (10)
≥5 to <10 years	108 (18)	79 (14)
≥10 to <15 years	106 (17)	113 (20)
≥15 to <20 years	56 (9)	77 (13)
≥20 to <25 years	80 (13)	68 (12)
≥25 years	187 (30)	179 (31)
Atopy, n (%)	311 (50)	270 (47)
Exacerbations in Previous Year		
Mean (SD)	3.6 (3.1)	3.6 (2.6)
Requiring ED visit/hospitalization, n (%)	271 (44)	190 (33)
Requiring hospitalization, n (%)	150 (24)	109 (19)
Maintenance Use OCS, n (%)	188 (31)	144 (25)
Mean Blood Eosinophils, cells/μL		
Geometric mean (Std logs)	250 (1.03)	290 (0.99)
Baseline Pre-bronchodilator % Predicted FEV_1		
Mean (SD)	59.7 (15.89)	61.0 (18.0)
Min, Max	18, 109	18, 128
Baseline Percent Reversibility FEV_1		
Mean (SD)	27.7 (22.38)	26.9 (21.5)
Min, Max	-8, 231	-13, 161
Baseline Pre-bronchodilator FEV_1/FVC ratio		
Mean (SD)	0.67 (0.15)	0.64 (0.13)
Min, Max	0.3, 2.5	0.3, 1.0
Baseline Asthma Control Questionnaire Score		
Mean (SD)	2.4 (1.1)	2.2 (1.2)

4.3.2. Patient Disposition

The majority of patients enrolled in the Exacerbation Studies completed the studies; 16% of patients in Study 997 and 6% in Study 588 prematurely withdrew (Table 7). Most patients (91%) who completed Study 588 elected to continue treatment in the available OLE Study 661. The most common reasons for withdrawal in both studies were withdrawal of consent, AEs, and lack of efficacy and these were balanced across the treatment groups.

Table 7 Patient Disposition (Studies 997 and 588, ITT Population)

Patient Status	Number (%) of Patients					
		Mepolizumab				
	Placebo	100mg SC	75mgIV	250mg IV	750mgIV	Total
Study 997	**N=155**	**---**	**N=153**	**N=152**	**N=156**	**N=616**
Completed	127 (82)	---	129 (84)	131 (86)	133 (85)	520 (84)
Withdrawn	28 (18)	---	24 (16)	21 (14)	23 (15)	96 (16)
Primary reason for withdrawal[1]						
Withdrew consent	11 (7)	---	8 (5)	2 (1)	7 (4)	28 (5)
Adverse event[2]	6 (4)	---	5 (3)	8 (5)	9 (6)	28 (5)
Lack of efficacy	8 (5)	---	6 (4)	4 (3)	4 (3)	22 (4)
Investigator discretion	1 (<1)	---	3 (2)	3 (2)	3 (2)	10 (2)
Lost to follow-up	1 (<1)	---	1 (<1)	4 (3)	0	6 (<1)
Protocol deviation	1 (<1)	---	1 (<1)	0	0	2 (<1)
Study 588	**N=191**	**N=194**	**N=191**	**---**	**---**	**N=576**
Completed	179 (94)	185 (95)	175 (92)	---	---	539 (94)
Withdrawn	12 (6)	9 (5)	16 (8)	---	---	37 (6)
Entered OLE Study 661	176 (92)	178 (92)	171 (90)	---	---	525 (91)
Primary reason for withdrawal[1]						
Withdrew consent	5 (3)	4 (2)	9 (5)	---	---	18 (3)
Adverse event[2]	4 (2)	1 (<1)	0	---	---	5 (<1)
Lack of efficacy	1 (<1)	2 (1)	1 (<1)	---	---	4 (<1)
Lost to follow-up	0	2 (1)	2 (1)	---	---	4 (<1)
Protocol deviation	0	0	3 (2)	---	---	3 (<1)
Investigator discretion	2 (1)	0	1 (<1)	---	---	3 (<1)

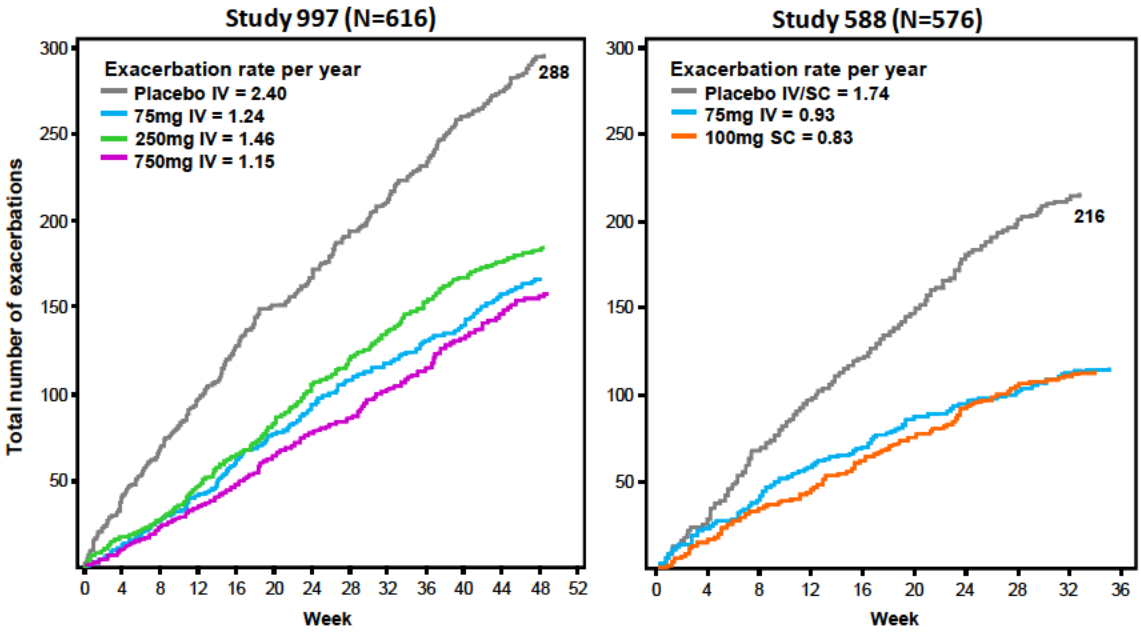
1. Only one primary reason for withdrawal was recorded
2. Patients with an AE leading to permanent discontinuation of study drug or withdrawal from the study

4.3.3. Asthma Exacerbations

Treatment with mepolizumab consistently resulted in statistically significant and clinically relevant reductions in the rate of exacerbations (defined in Section 3.3.1.1) compared with placebo regardless of route of administration. In both Studies 997 and 588, all doses of mepolizumab consistently decreased the number of exacerbations by approximately 50%, and a separation of treatment response was observed within the first 8 weeks of treatment (Figure 7). A consistent reduction of exacerbations with each IV dose across the 10-fold dose range was observed in Study 997. Based on the cumulative number of exacerbations in the placebo group (288 in Study 997 over 52 weeks and 216 in Study 588 over 32 weeks), it is evident that patients receiving high dose ICS plus an additional asthma controller were not well controlled despite receiving existing optimized standard of care. Thus, a reduction in exacerbations of this magnitude with mepolizumab is substantial and clinically meaningful.

Additionally, the temporal exacerbation pattern was only marginally impacted by season. This observation suggests that patients with severe eosinophilic asthma have chronic inflammation and exacerbations that are not primarily triggered by seasonal insults [Ortega, 2014].

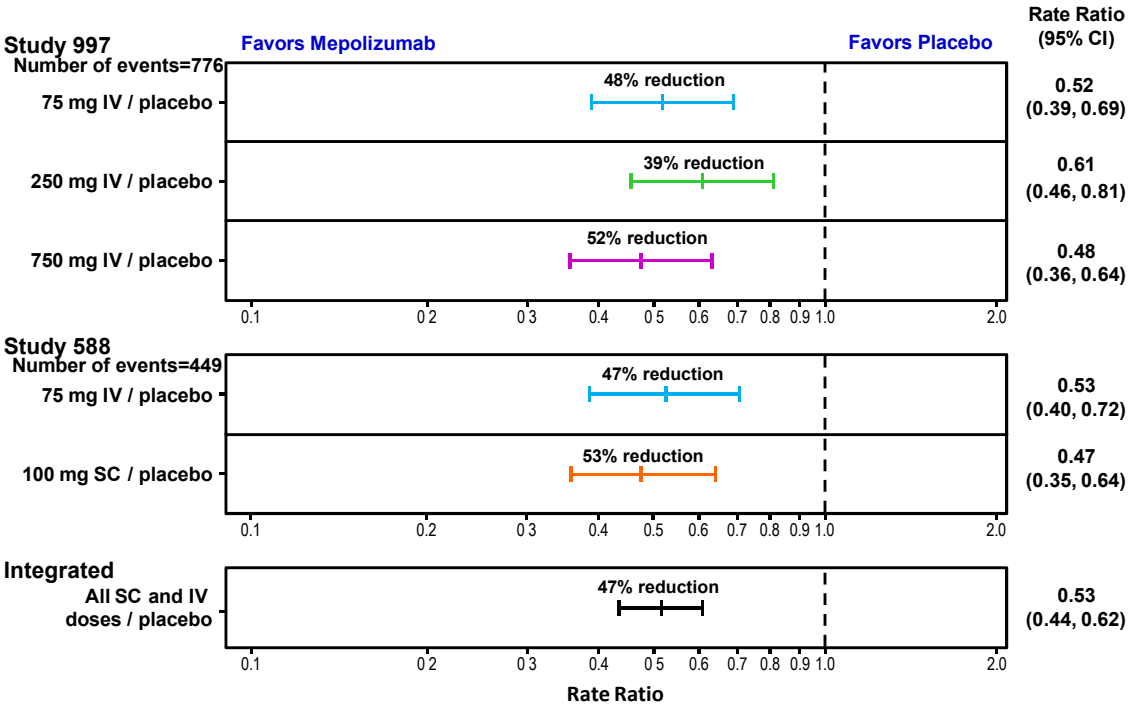
Figure 7 **Cumulative Exacerbations Over Time (Studies 997 and 588, ITT Population)**



Exacerbations were defined as worsening of asthma which required intervention with oral or systemic corticosteroids and may have required an emergency department visit or hospitalization

In Studies 997 and 588, all doses and routes of administration showed statistically significant reductions in exacerbations compared with placebo: reductions in exacerbations of 48% and 47% were observed with 75 mg IV in Studies 997 and 588, respectively, and a 53% reduction with 100 mg SC in Study 588 (Figure 8). Study 588 replicated the results of the 75 mg IV dose in Study 997 and showed that the efficacy of mepolizumab 100 mg SC was similar to 75 mg IV.

Figure 8 Analysis of Rate of Exacerbations: Ratio to Placebo (Studies 997 and 588, ITT Population)



4.3.3.1. Missing Data

For the primary endpoint of exacerbations, for patients who withdrew, all data up to the time of patient withdrawal are included in the analyses; however, there are missing data for the period following withdrawal. Patient withdrawals are presented in Section 4.3.2.

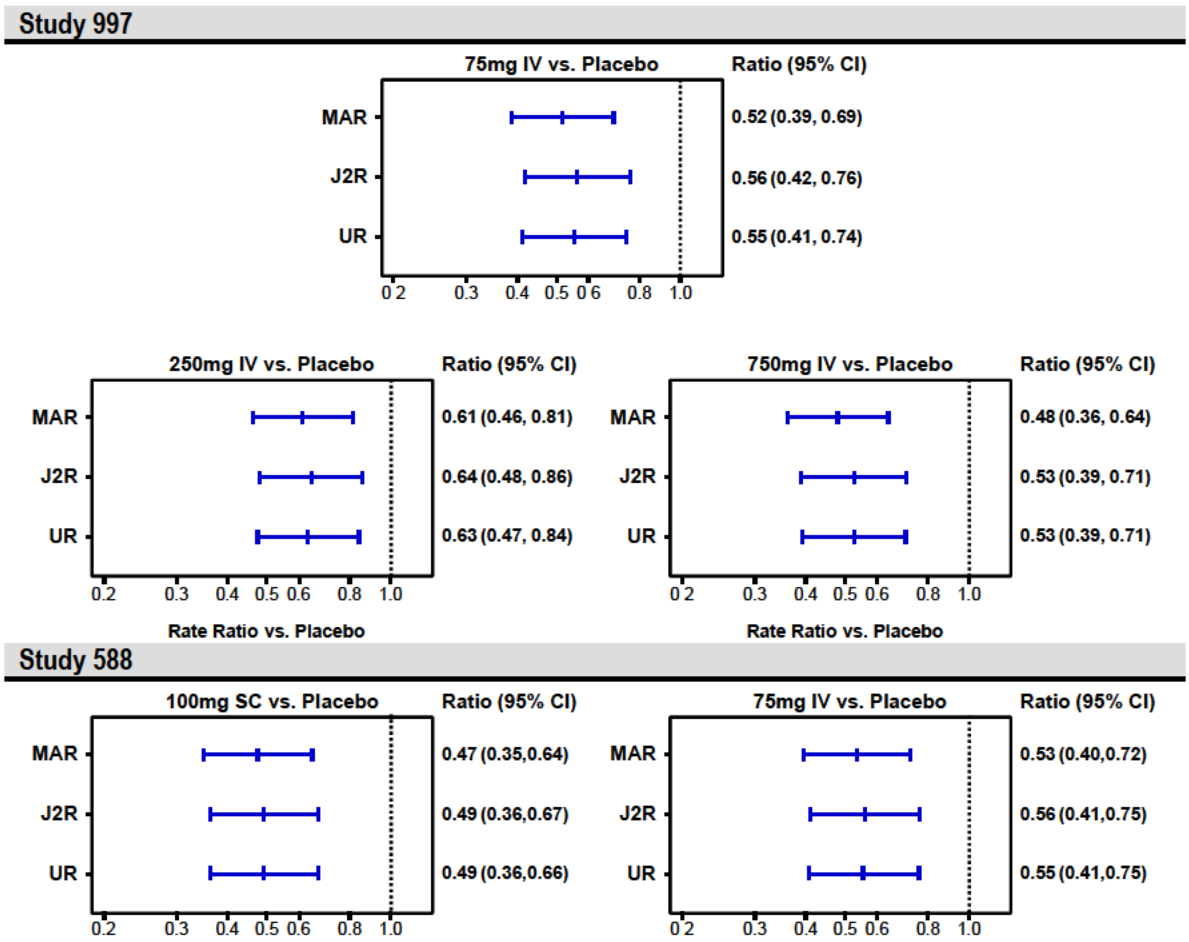
The primary analysis made a standard assumption known as the Missing At Random (MAR) assumption. This assumes that future exacerbations for those who withdraw can be predicted from their exacerbation history prior to withdrawal and from the exacerbation rate of similar patients on the same treatment.

In order to understand how different assumptions regarding missing data could affect the results, two key sensitivity analyses were performed. In both of these sensitivity analyses, it is assumed that future exacerbations for patients who withdrew from a mepolizumab arm could be predicted based on the exacerbation rate in the placebo arm, not on the mepolizumab arm.

In the first sensitivity analysis, Jump to Reference (J2R), future exacerbations for all patients who withdraw (whether mepolizumab or placebo) are predicted based on the exacerbation rate in the placebo arm only and depend on the exacerbation history for a patient prior to withdrawal. The Unconditional Reference (UR) analysis also predicts future exacerbations for all patients who withdraw based on the exacerbation rate in the placebo arm only, but views withdrawal as a new event for the patient and does not take into account the exacerbation history for a patient prior to withdrawal when predicting future exacerbations.

Both of these sensitivity analyses make only a small change to the estimated rate reduction for mepolizumab compared with placebo and all comparisons remain highly significant (Figure 9).

Figure 9 Sensitivity Analyses of Rate of Exacerbations: Ratio to Placebo (Studies 997 and 588, ITT Population)



MAR = Missing at Random, J2R = Jump to Reference, UC = Unconditional Reference

4.3.3.2. Exacerbations Requiring Emergency Department Visits and/or Hospitalization

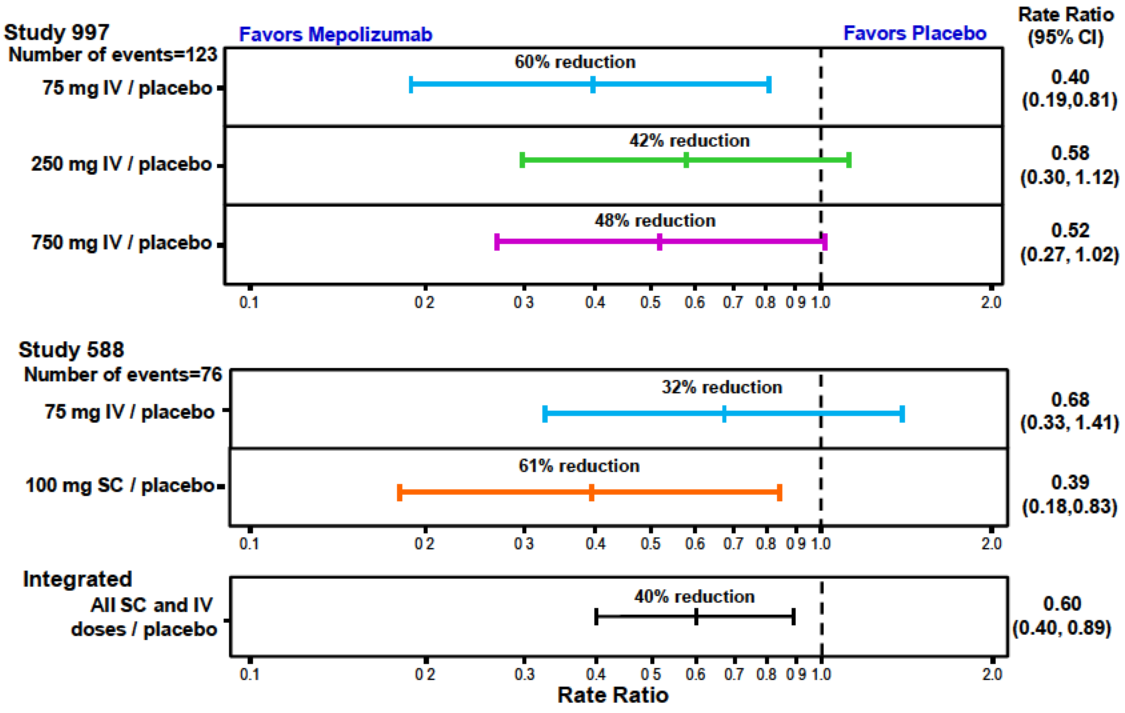
Severe exacerbations requiring ED visits and/or hospitalization occurred less frequently than the primary outcome. Due to the low number of events, reductions in these more severe exacerbations would not necessarily be detected as statistically significant, but are considered clinically relevant.

Mepolizumab consistently reduced the rate of severe exacerbations requiring ED visits and/or hospitalization compared with placebo (Table 8 and Figure 10). For exacerbations requiring ED visits and/or hospitalization, a decrease of 61% compared with placebo was observed with 100 mg SC (p=0.015) in Study 588 and decreases of 60% and 32% were observed with 75 mg IV (p=0.011 and p=0.299) in Studies 997 and 588, respectively.

Table 8 **Rate of Exacerbations Requiring Hospitalization/ED Visits (Studies 997 and 588, ITT Population)**

Study 997				
	Placebo N=155	75 mg IV N=153	250 mg IV N=152	750 mg IV N=156
Number of exacerbations	44	19	32	28
Exacerbation rate/year	0.43	0.17	0.25	0.22
Study 588				
	Placebo N=191	75 mg IV N=194	100 mg SC N=191	
Number of exacerbations	33	23	20	
Exacerbation rate/year	0.20	0.14	0.08	
Study 997 + Study 588				
	Placebo N=346	All Doses N=846		
Number of exacerbations	77	122		
Exacerbation rate/year	0.26	0.16		

Figure 10 **Exacerbations Requiring Emergency Department Visit and/or Hospitalization (Studies 997 and 588, ITT Population)**

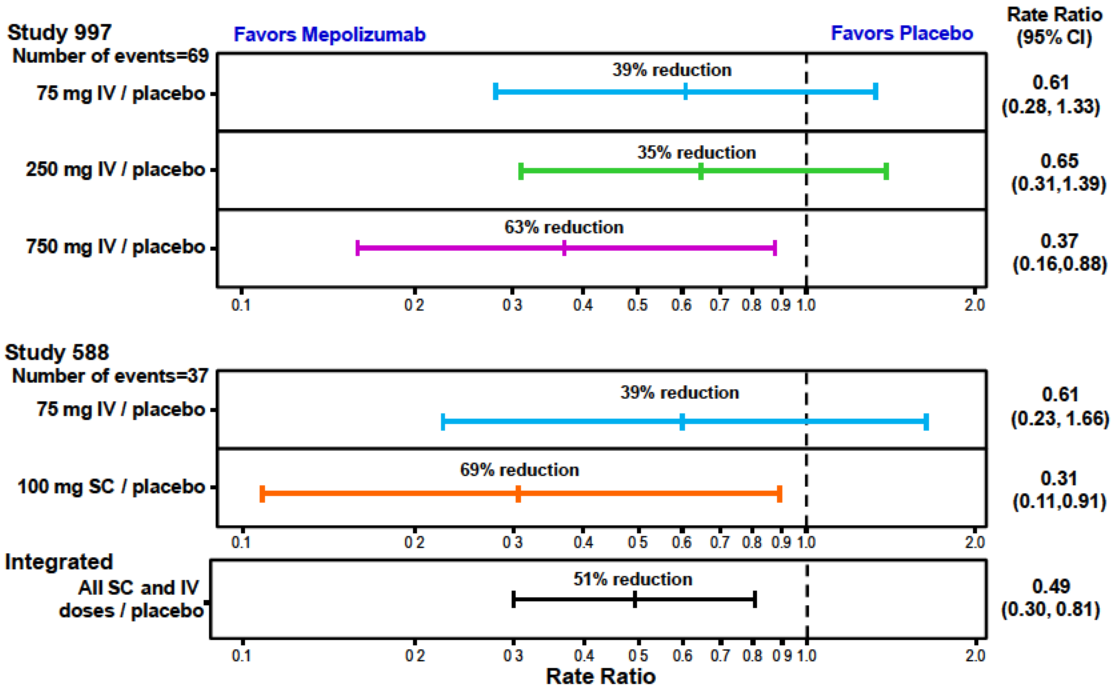


For exacerbations requiring only in-patient hospitalization, an even smaller subset of events, a decrease of 69% compared with placebo was observed with 100 mg SC (p=0.034) in Study 588 and decreases of 39% were observed with 75 mg IV (p=0.214 and p=0.334) in Study 997 and Study 588, respectively (Table 9 and Figure 11).

Table 9 **Rate of Exacerbations Requiring Hospitalization (Studies 997 and 588, ITT Population)**

Study 997				
	Placebo N=155	75 mg IV N=153	250 mg IV N=152	750 mg IV N=156
Number of exacerbations	27	15	17	10
Exacerbation rate/year	0.18	0.11	0.12	0.07
Study 588				
	Placebo N=191	75 mg IV N=194	100 mg SC N=191	
Number of exacerbations	18	10	9	
Exacerbation rate/year	0.10	0.06	0.03	
Study 997 + Study 588				
	Placebo N=346	All Doses N=846		
Number of exacerbations	45	61		
Exacerbation rate/year	0.14	0.07		

Figure 11 **Exacerbations Requiring Hospitalization (Studies 997 and 588, ITT Population)**

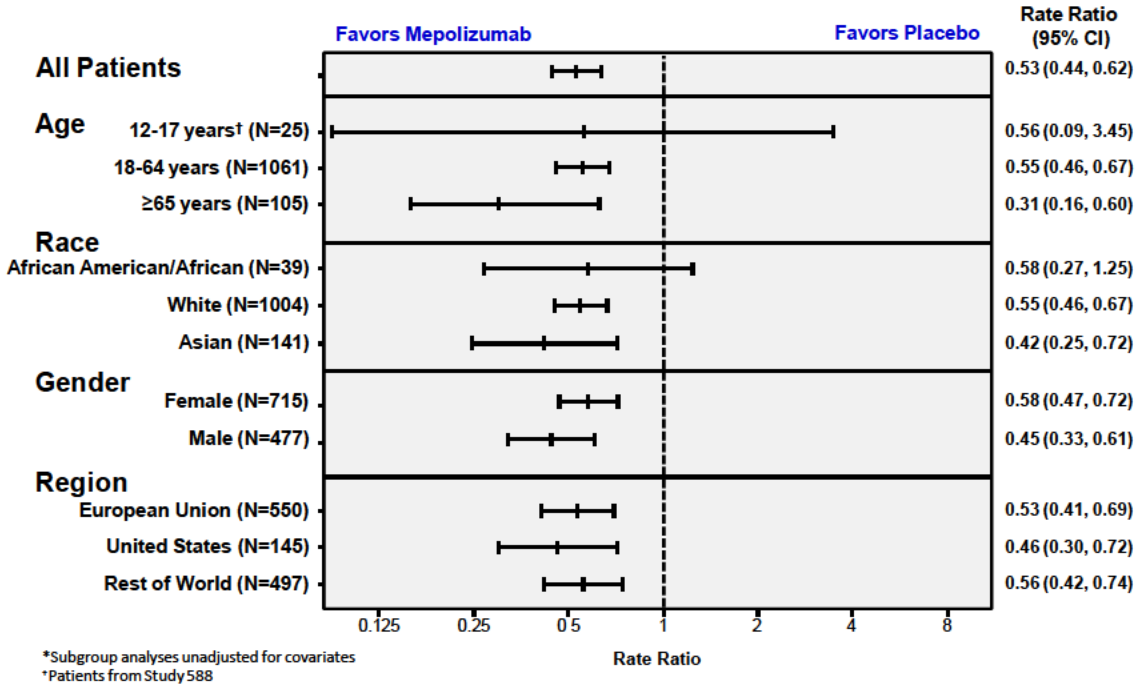


Overall, these results show that treatment with mepolizumab produced clinically relevant reductions in the rate of severe exacerbations resulting in ED visits and hospitalization and in the rate of severe exacerbations requiring hospitalization.

4.3.3.3. Subgroup Analyses of Exacerbations

Subgroup analyses are not designed to demonstrate statistical significance for the effect of mepolizumab over placebo; however, they can illustrate consistency of the overall treatment effect. The frequency of exacerbations was examined by subgroups of age, race, gender, and geographic region. Study 997 only included one adolescent patient, thus the analysis by age for patients 12-17 years is based on Study 588 alone. Regardless of demographic characteristic or region, patients treated with mepolizumab had a lower rate of exacerbations compared with patients treated with placebo (Figure 12).

Figure 12 Subgroup Analyses* of Exacerbations by Demographic Characteristics and Geographic Region (Studies 997 and 588, ITT Population)



Although enrollment of adolescents and patients of African heritage was low, these subgroups showed a similar treatment response compared with the overall population. In addition, following either IV or SC administration, both subgroups displayed plasma concentrations and predicted clearance within the range of the rest of the study population.

4.3.4. Quality of Life

4.3.4.1. Asthma Quality of Life Questionnaire (AQLQ)

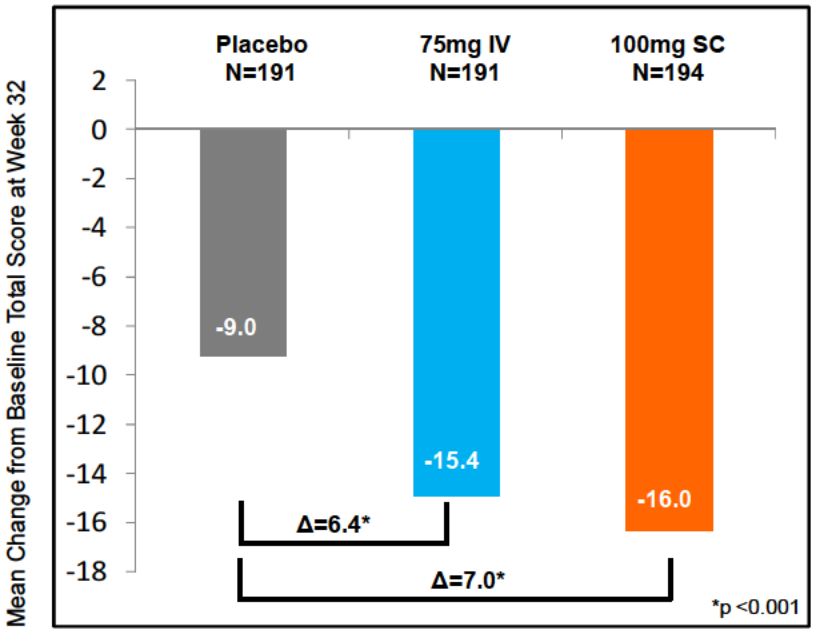
Study 997 used the AQLQ (described in Section 3.3.1.4) to assess patient health-related quality of life. Baseline mean scores were similar across the treatment groups: 4.1 in the placebo group, and 4.2 in each of the mepolizumab groups. At Week 52, small non-significant improvements in AQLQ score were observed with mepolizumab; mean differences from placebo were 0.08, 0.05, and 0.22 points for the 75, 250 and 750 mg IV

dose groups, respectively. Similar proportions of patients in each treatment group achieved changes in AQLQ score that met or exceeded the MCID of 0.5 points (46% in the placebo group and 47% in each mepolizumab group).

4.3.4.2. St. George's Respiratory Questionnaire (SGRQ)

Study 588 utilized the SGRQ (described in Section 3.3.1.4) for patient assessment of health-related quality of life. Mean scores at baseline were similar across the treatment groups: 46.9, 44.4, and 47.9 in the placebo, mepolizumab 75 mg IV, and mepolizumab 100 mg SC groups, respectively. Patients treated with mepolizumab 75 mg IV and 100 mg SC showed statistically significant improvements over placebo ($p<0.001$) in the SGRQ total score after 32 weeks: -6.4 and -7.0 points for mepolizumab 75 mg IV and 100 mg SC, respectively (Figure 13). These treatment differences exceeded the MCID for this instrument (-4.0 point reduction).

Figure 13 Analysis of Change from Baseline in SGRQ Total Score at Week 32 (Study 588, ITT Population)



For Δ=6.4, 95% CI (3.2, 9.7) and for Δ=7.0, 95% CI (3.8, 10.2)

4.3.4.3. Response to Therapy Assessment

Quality of life improvements were also evident in overall evaluation of response to therapy as rated by the clinician and the patient in both Exacerbation Studies. At the end of the respective treatment periods, whether self-rated or clinician-rated, more patients treated with mepolizumab 100 mg SC or 75 mg IV showed greater observable improvement (higher odds of being in a better category) compared with patients treated with placebo ($p\leq0.003$) (Table 10). Clinician- and patient-rated response to therapy evaluations were also statistically significant for the 250 mg and 750 mg IV dose groups in Study 997 ($p\leq0.005$).

Table 10 Summary of Clinician-Rated and Patient-Rated Overall Evaluation of Response to Therapy at the End of Treatment (Studies 997 and 588, ITT Population)

	Clinician Rating			Patient Rating		
Rating	Placebo	Mepo 100mg SC	Mepo 75mg IV	Placebo	Mepo 100mg SC	Mepo 75mg IV
Study 997 - Week 52						
n	155	---	153	155	---	153
1 (Significant. improved)	23 (15)	---	46 (30)	33 (21)	---	56 (37)
2 (Moderately improved)	29 (19)	---	23 (15)	27 (17)	---	26 (17)
3 (Mildly improved)	24 (15)	---	30 (20)	29 (19)	---	24 (16)
4 (No change)	46 (30)	---	34 (22)	35 (23)	---	25 (16)
5 (Mildly worse)	6 (4)	---	0	3 (2)	---	2 (1)
6 (Moderately worse)	1 (<1)	---	1 (<1)	1 (<1)	---	1 (<1)
7 (Significantly worse)	1 (<1)	---	1 (<1)	2 (1)	---	1 (<1)
Missing	25 (16)	---	18 (12)	25 (16)	---	18 (12)
Odds ratio to placebo	---	---	1.94	--	---	1.84
(95% CI)	---	---	(1.30, 2.91)	---	---	(1.23, 2.75)
p-value	---	---	0.001	---	---	0.003
Study 588 - Week 32						
n	191	194	191	191	194	191
1 (Significant. improved)	18 (9)	60 (31)	44 (23)	37 (19)	78 (40)	57 (30)
2 (Moderately improved)	39 (20)	56 (29)	51 (27)	31 (16)	48 (25)	43 (23)
3 (Mildly improved)	44 (23)	35 (18)	41 (21)	40 (21)	30 (15)	34 (18)
4 (No change)	71 (37)	32 (16)	36 (19)	63 (33)	26 (13)	40 (21)
5 (Mildly worse)	5 (3)	1 (<1)	2 (1)	6 (3)	3 (2)	2 (1)
6 (Moderately worse)	1 (<1)	1 (<1)	2 (1)	2 (1)	0	1 (<1)
7 (Significantly worse)	0	0	1 (<1)	0	0	1 (<1)
Missing	13 (7)	9 (5)	14 (7)	12 (6)	9 (5)	13 (7)
Odds ratio to placebo	---	3.29	2.10	---	2.98	1.74
(95% CI)	---	(2.28, 4.76)	(1.46, 3.02)	---	(2.06, 4.32)	(1.21, 2.50)
p-value	---	<0.001	<0.001	---	<0.001	0.003

4.3.5. Asthma Control

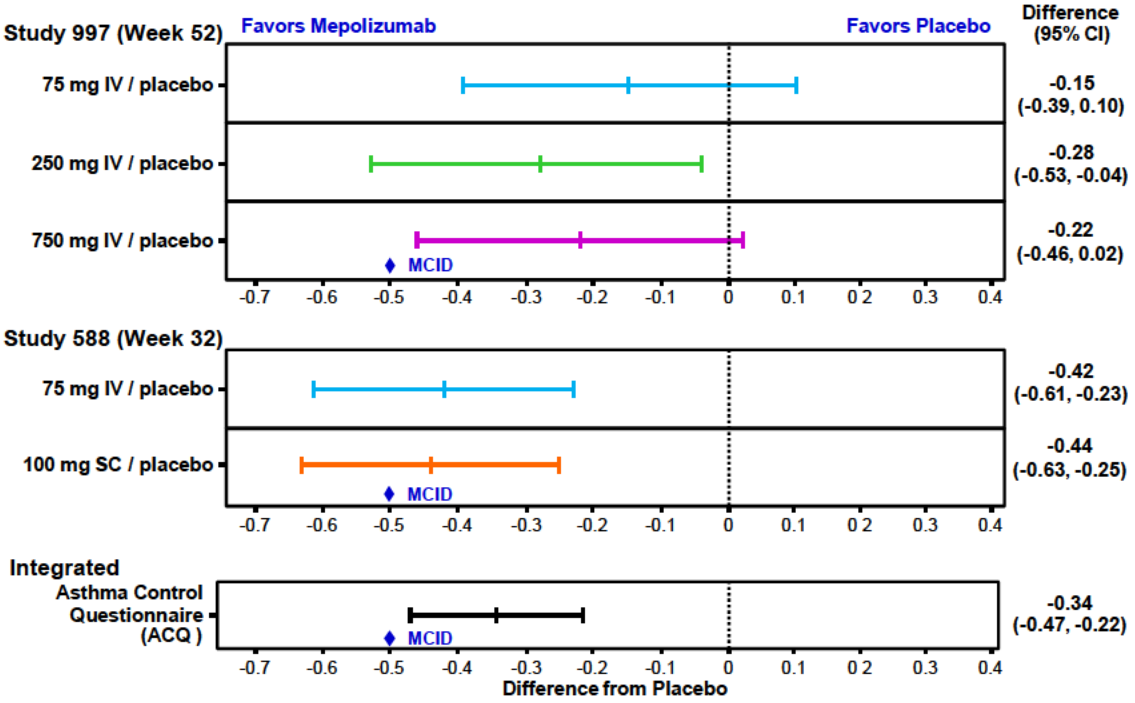
In both Exacerbation Studies, mean baseline ACQ scores were >1.5 (2.4 in Study 997 and 2.2 in Study 588)), indicating poor asthma control even through patients were receiving optimized standard of care. At the end of the treatment periods, ACQ scores were improved with mepolizumab, particularly in Study 588, where difference with placebo approached the commonly accepted MCID of 0.5 (Figure 14).

In Study 997, a small improvement over placebo was seen in the ACQ score with mepolizumab 75 mg IV over the duration of the study which was not statistically significant at Week 52 (-0.15; p=0.232). Statistical significance was however observed with the 250 mg IV dose (-0.28; p=0.023).

In Study 588, mepolizumab produced larger improvements in the ACQ score compared with placebo over the duration of the study. At Week 32, treatment differences with placebo were statistically significant and approached the MCID threshold of -0.5:

-0.44 for 100 mg SC and -0.42 for 75 mg IV (p<0.001). The percentage of patients achieving the MCID improvement on an individual basis was 45% for placebo, 48% for mepolizumab 75mg IV and 57% for mepolizumab 100mg SC.

Figure 14 Repeated Measures Analysis of Change from Baseline in ACQ Score (Studies 997 and 588, ITT Population)



4.3.6. Lung Function

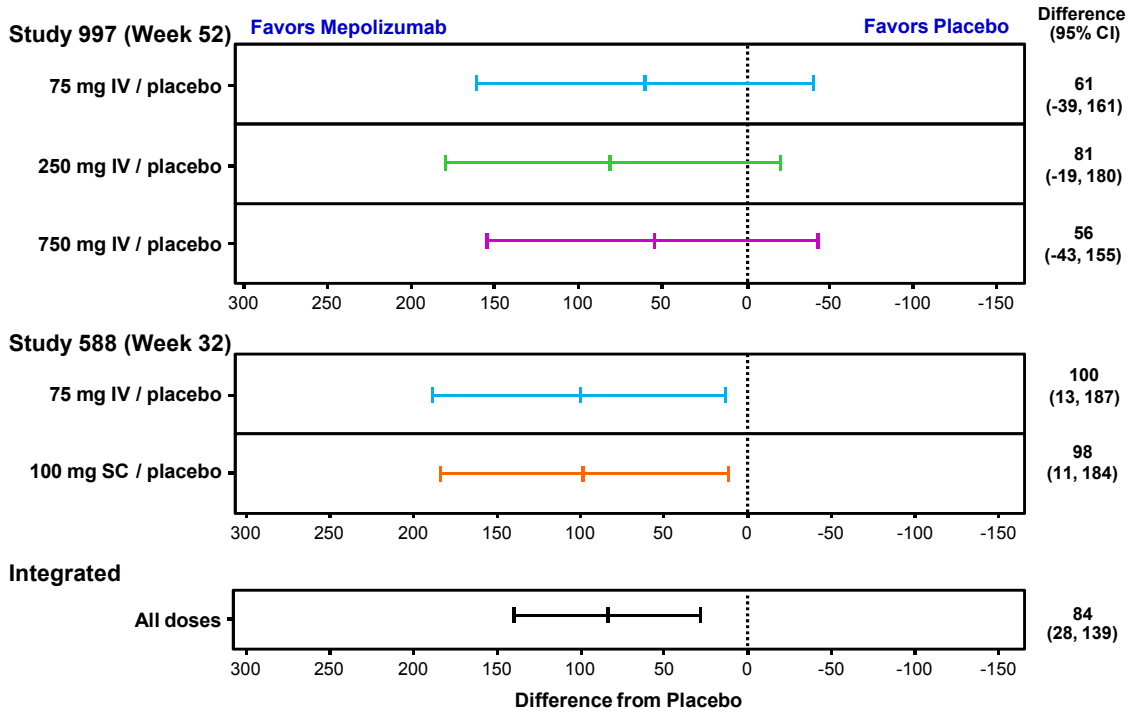
4.3.6.1. FEV_1

Pre-bronchodilator FEV_1

In Study 997, an improvement of 61 mL in pre-bronchodilator FEV_1 was observed with mepolizumab 75 mg IV compared with placebo at the end of the 52-week treatment period (Figure 15). Similar differences were also noted at the higher doses at Week 52; none was statistically significant.

In Study 588, larger improvements in pre-bronchodilator FEV_1 were observed with mepolizumab compared with placebo over the duration of the study. At the end of the 32-week treatment period, treatment differences with 75 mg IV and 100 mg SC were 100 mL (p=0.025) and 98 mL (p=0.028) (Figure 15). These changes are clinically important considering that this severe population with long duration of their disease is on maximal standard of care, including high-dose ICS and/or OCS.

Figure 15 Analysis of Change from Baseline in Pre-Bronchodilator FEV_1 (mL) (Studies 997 and 588, ITT Population)



Post-bronchodilator FEV_1

In Study 997, improvements in post-bronchodilator FEV_1 were of similar magnitude to those observed for pre-bronchodilator FEV_1. At Week 52, differences from placebo were 45 mL (95% CI: -50 to 139; p=0.356); 89 mL (95% CI: -6 to 184; p=0.066) and 78 mL (95% CI: -16 to 172; p=0.105) in the mepolizumab 75 mg, 250 mg and 750 mg groups, respectively. None of these changes were statistically significant.

In Study 588 at Week 32, patients treated with both mepolizumab doses showed marked improvements from baseline in post-bronchodilator FEV_1 compared with the placebo group: 138 mL (95% CI: 43, 232; p=0.004) and 146 mL (95% CI: 50, 242; p=0.003) in the mepolizumab 100 mg SC and 75 mg IV groups, respectively.

4.3.6.2. Peak Expiratory Flow

Similar to the pattern of FEV_1 response in Study 997, non-significant improvements in PEF of <10 L/min were seen over the course of the study for mepolizumab compared with placebo.

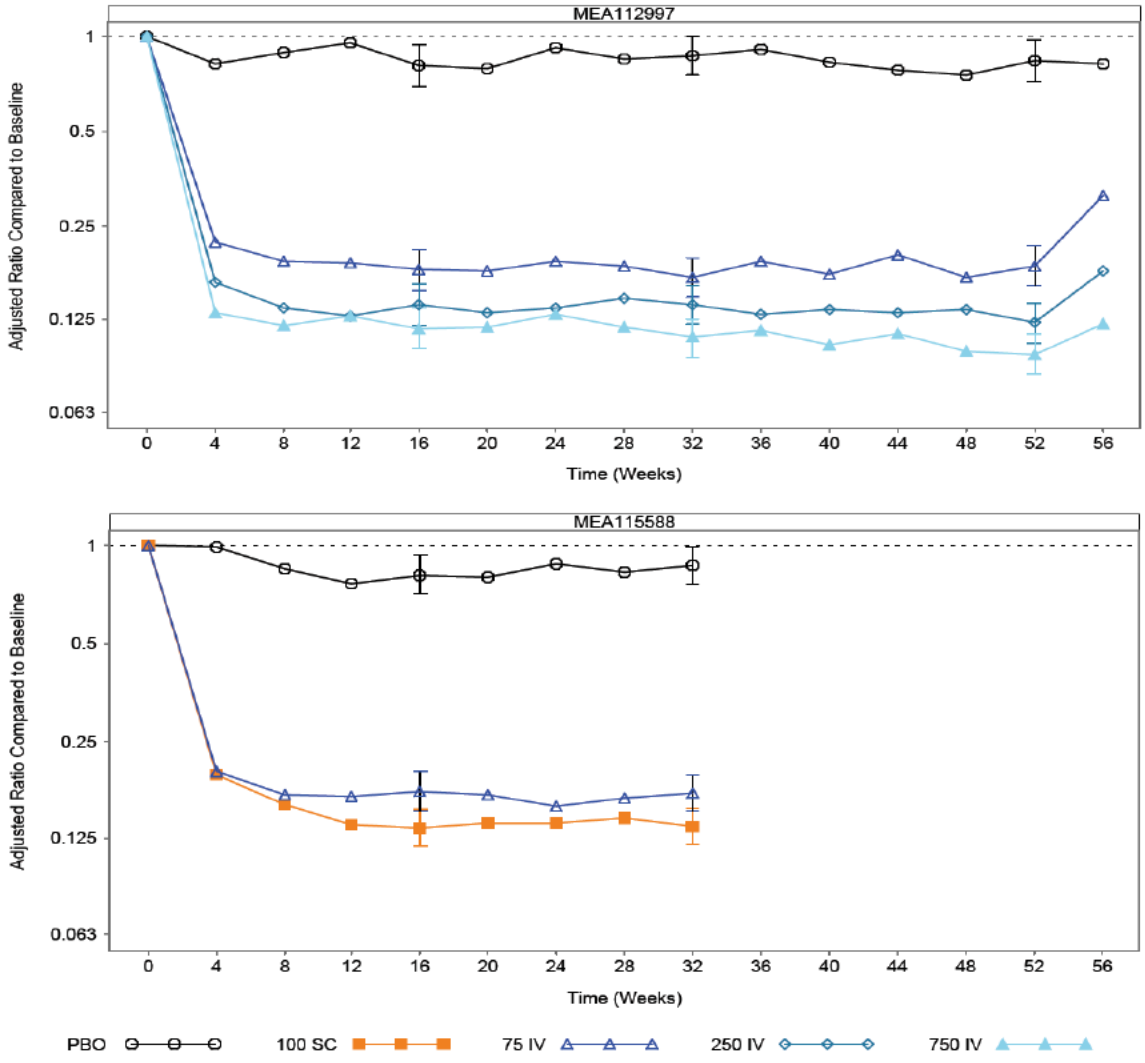
In Study 588, consistent improvements from baseline in morning PEF were observed with mepolizumab, further supporting improved lung function in this study. Overall increases of 14.9 to 32.3 L/min and 12.0 to 25.0 L/min were observed for 100 mg SC and for 75 mg IV, respectively, compared with -1.5 to 8.1 L/min for placebo. The improvement in PEF observed with mepolizumab is consistent with previously reported changes considered clinically relevant [Santanello, 1999]. The pre-defined analysis plan

for this study did not include statistical comparison of mepolizumab treatment compared with placebo.

4.3.7. Eosinophils

Treatment with mepolizumab 100 mg SC or 75 mg IV resulted in rapid reduction of blood eosinophils (approximately 80% by the first assessment at Week 4) which was sustained over the duration of treatment in the Exacerbation Studies (Figure 16); Reductions in eosinophil counts from means of 250-290 cells/μL to 60 cells/μL were observed. Due to the targeted mechanism of action, eosinophil reduction is not complete allowing for some background host surveillance to maintain homeostasis.

Figure 16 Ratios to Baseline in Blood Eosinophils over Time (Studies 997 and 588, ITT Population)



Note: Vertical bars represent 95% CIs.
Note: Where a result of zero was recorded, a small value (i.e., minimum of all non-missing results/2) was added prior to log transformation.

4.4. OCS Reduction Study 575

Patients with severe eosinophilic asthma have a significant burden of regular corticosteroid use, which often leads to untoward effects associated with the chronic use of prednisone (see Section 2.1). In this severe patient population, reduction of oral corticosteroid use is an additional key treatment outcome as well as achieving asthma control.

4.4.1. Demographics and Baseline Characteristics

4.4.1.1. Demographics

Demography and baseline characteristics of patients in Study 575 were consistent with the population in the Exacerbation Studies. The patients in this study were primarily White (95%), more than half were female (55%), the mean age was 50 years, and patients had an elevated BMI (28.7 kg/m^2) (Table 11). Demography was comparable between the treatment groups, except for a larger proportion of females in the mepolizumab group (64%) compared with the placebo group (45%).

Table 11 Demographics (Study 575, ITT Population)

Demographic	Placebo N=66	Mepolizumab 100 mg SC N=69	Total N=135
Gender, n (%)			
Female	30 (45)	44 (64)	74 (55)
Male	36 (55)	25 (36)	61 (45)
Age, yr			
Mean (SD)	49.9 (10.30)	49.8 (14.10)	49.9 (12.34)
Min, Max	28, 70	16, 74	16, 74
Age Group, n (%)			
12-17 years	0	2 (3)	2 (1)
18-64 years	60 (91)	59 (86)	119 (88)
≥65 years	6 (9)	8 (12)	14 (10)
Race, n (%)			
White	61 (92)	67 (97)	128 (95)
Asian	2 (3)	1 (1)	3 (2)
American Indian or Alaskan Native	1 (2)	0	1 (<1)
Native Hawaiian or Pacific Islander	1 (2)	0	1 (<1)
Other (Mixed Race)	1 (2)	1 (1)	2 (1)
Ethnicity, n (%)			
Not Hispanic/Latino	63 (95)	67 (97)	130 (96)
Hispanic/Latino	3 (5)	2 (3)	5 (4)
Body Mass Index, kg/m^2			
Mean (SD)	29.52 (6.047)	27.84 (5.895)	28.66 (6.007)
Min, Max	20.0, 52.1	19.7, 48.8	19.7, 52.1

4.4.1.2. Baseline Characteristics

Patients in Study 575 also had long duration of asthma with a mean of approximately 19 years; nearly half were atopic (Table 12). Mean baseline blood eosinophil counts in the placebo and mepolizumab groups were 230 and 250 cells/μL, respectively. Of note, these baseline eosinophil counts were relatively similar to those reported in the Exacerbation Studies (see Section 4.3.1.2). Despite being treated with optimized standard of care, including OCS, patients had a mean of 3 exacerbations in the previous year and baseline ACQ scores (1.99 and 2.15) exceeded the cut-off of 1.5, indicating uncontrolled disease. Lung function results were consistent with this severe disease phenotype.

Table 12 Asthma History (Study 575, ITT Population)

Asthma History	Placebo N=66	Mepolizumab 100 mg SC N=69
Duration of Asthma, yr		
Mean (SD)	20.1 (14.37)	17.4 (11.79)
Median	18.5	15.0
Min, Max	1, 58	2, 55
Duration of Asthma Category, n (%)		
≥1 to <5 years	10 (15)	7 (10)
≥5 to <10 years	9 (14)	16 (23)
≥10 to <15 years	8 (12)	6 (9)
≥15 to <20 years	12 (18)	11 (16)
≥20 to <25 years	5 (8)	10 (14)
≥25 years	22 (33)	19 (28)
Atopy, n (%)	34 (52)	28 (41)
Exacerbations in Previous Year		
Mean (SD)	2.9 (2.76)	3.3 (3.39)
Min, Max	0, 13	0, 16
Blood Eosinophil Count (cells/μL)		
Geometric mean (Std logs)	230 (1.00)	250 (1.25)
Baseline Pre-bronchodilator % predicted FEV_1		
Mean (SD)	57.8 (18.54)	59.6 (17.04)
Min, Max	15, 93	18, 94
Baseline Percent Reversibility FEV_1		
Mean (SD)	24.7 (18.10)	27.3 (17.38)
Min, Max	-5, 94	-2, 71
Baseline Pre-bronchodilator FEV_1/FVC Ratio		
Mean (SD)	0.61 (0.117)	0.63 (0.124)
Min, Max	0.3, 0.8	0.3, 0.9
Baseline Asthma Control Questionnaire Score		
Mean (SD)	1.99 (1.175)	2.15 (1.268)

Nearly half of the patients in this study had been taking oral corticosteroids for more than 5 years; median daily OCS doses at screening were 15.0 mg in the placebo group and 12.5 mg in the mepolizumab group (Table 13). After the Optimization Phase, median

daily OCS doses were adjusted to 12.5 mg and 10 mg (i.e., Baseline doses), respectively. As noted in Section 2.1, daily doses of OCS >5 mg are associated with both short- and long-term systemic effects.

Table 13 OCS History and Baseline Dose (Study 575, ITT Population)

OCS History and Baseline Dose	Placebo N=66	Mepolizumab 100 mg SC N=69
Duration of OCS Use at Baseline[1], n (%)		
<5 years	35 (53)	35 (51)
≥5 years	31 (47)	34 (49)
Screening Daily OCS Dose[2]		
Mean (SD), mg	15.2 (6.71)	15.1 (9.31)
Median	15.0	12.5
Min, Max	5, 35	5, 35
Optimized (Baseline) OCS Dose[3]		
Mean (SD), mg	13.2 (6.26)	12.4 (7.17)
Median	12.5	10.0
Min, Max	5, 35	5, 35

1. Actual strata; 7 patients were randomized into the incorrect strata
2. Post-hoc analysis for manuscript
3. Optimized dose at Visit 3/Randomization

4.4.2. Patient Disposition

The majority of patients completed the study (95%) and continued treatment in the OLE Study 661 (93%) (Table 14). The withdrawal rate was low (5%) and was primarily due to AEs.

Table 14 Patient Disposition (Study 575, ITT Population)

Patient Status	Number (%) of Patients		
	Placebo N=66	Mepolizumab 100 mg SC N=69	Total N=135
Completed	62 (94)	66 (96)	128 (95)
Withdrawn	4 (6)	3 (4)	7 (5)
Entered OLE Study 661[1]	61 (92)	65 (94)	126 (93)
Primary reason for withdrawal[2]			
Adverse event[3]	3 (5)	3 (4)	6 (4)
Withdrew consent	1 (2)	0	1 (<1)

1. Two patients elected not to continue in the OLE study after these data were provided.
2. Only one primary reason for withdrawal was recorded.
3. Patients with an AE leading to permanent discontinuation of study drug or withdrawal from the study

4.4.3. OCS Reduction Endpoints

Mepolizumab demonstrated statistically significant and clinically relevant improvements compared with placebo for key endpoints of OCS reduction.

The primary endpoint of the study was the percent reduction from baseline in daily prednisone use by defined dose reduction category. Patients treated with mepolizumab had a 2.4 times greater odds of achieving a category of greater daily OCS reduction, while maintaining asthma control, compared with those treated with placebo; this difference was statistically significant (p=0.008) (Table 15).

Table 15 Analysis of OCS Percent Reduction from Baseline during Weeks 20-24 by Reduction Categories (Study 575, ITT Population)

Percent Reduction from Baseline	Number (%) of Patients	
	Placebo N=66	Mepolizumab 100 mg SC N=69
n	66	69
90% to 100%	7 (11)	16 (23)
75% to <90%	5 (8)	12 (17)
50% to <75%	10 (15)	9 (13)
>0% to <50%	7 (11)	7 (10)
No decrease in OCS, lack of asthma control, or withdrawal from treatment	37 (56)	25 (36)
Odds ratio to placebo	---	2.39
95% CI	---	(1.25, 4.56)
p-value	---	0.008

Note: Analyzed using a proportional odds model (multinomial [ordered] logistic generalized linear model), with terms for treatment group, region, duration of OCS use at baseline (<5 yrs vs. ≥5 yrs), and baseline OCS dose (optimized dose).

Secondary OCS reduction endpoints were consistent in demonstrating the benefit of mepolizumab in enabling the reduction of OCS dose (Table 16). During Weeks 20-24, more than half of patients treated with mepolizumab (54%) achieved: 1) at least a 50% reduction in OCS dose compared with 33% receiving placebo, and 2) a reduction of OCS dose to ≤5.0 mg compared with 32% treated with placebo; both endpoints were statistically significant.

More patients treated with mepolizumab achieved a complete (100%) reduction in OCS dose compared with those treated with placebo, but the number of patients with this outcome was small (10 vs. 5 patients) and the difference was not statistically significant.

Additionally, during Weeks 20 to 24, patients treated with mepolizumab achieved a significant median percentage reduction of 50% from baseline in daily OCS dose versus 0% for those treated with placebo. From the start of the study to the end of the study, a marked reduction in median daily OCS doses was observed in the mepolizumab group (from 10.0 mg to 3.1 mg) in contrast to only a modest reduction in the placebo group (from 12.5. mg to 10 mg).

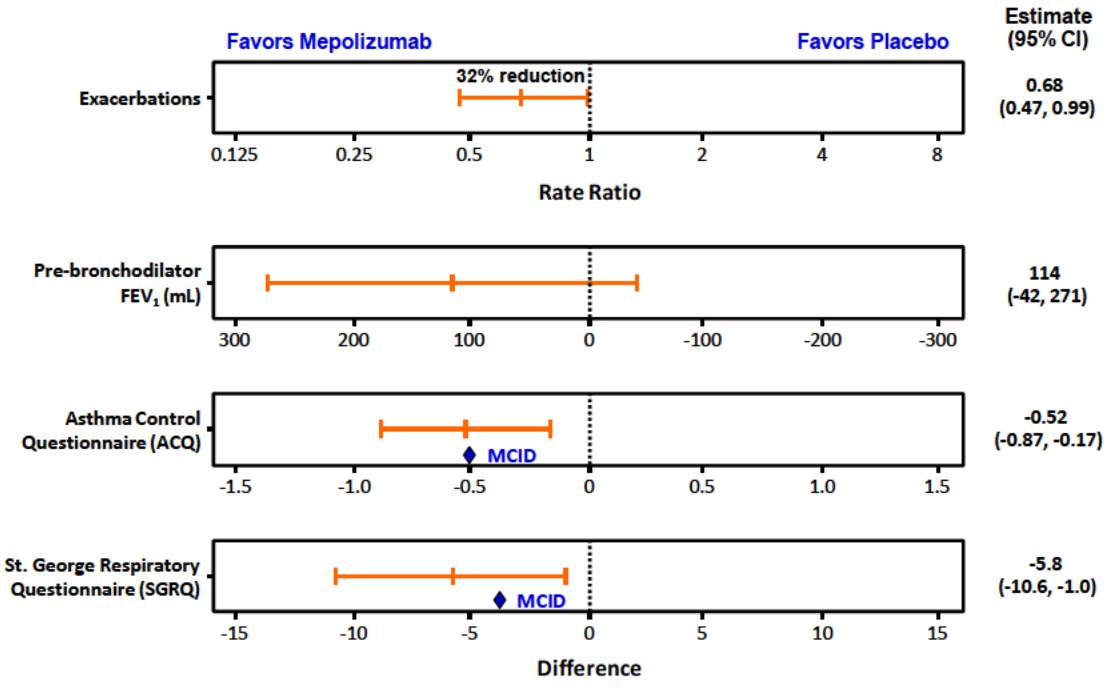
Table 16 Secondary OCS Reduction Endpoints Weeks 20-24 (Study 575, ITT Population)

Secondary Endpoint	Placebo N=66	Mepo 100 mg SC N=69	p-value
Reduction of ≥50% in daily OCS dose, n (%)	22 (33)	37 (54)	0.027
Reduction of daily OCS dose to ≤5.0 mg, n (%)	21 (32)	37 (54)	0.025
Complete reduction of OCS dose, n (%)	5 (8)	10 (14)	0.414
Median % reduction from baseline in daily OCS dose	0	50	0.007
Median OCS Dose, mg			
Start of treatment	12.5	10.0	---
End of the study	10.0	3.1	---

4.4.4. Other Endpoints

Even while reducing OCS dose, patients treated with mepolizumab 100 mg SC experienced greater improvements in other efficacy and quality of life endpoints compared with those treated with placebo (standard of care). These positive results further support the benefits of mepolizumab in an OCS-dependant population (Figure 17).

Figure 17 Other Endpoints (Study 575, ITT Population)



4.4.4.1. Asthma Exacerbations

Reduction in the rate of exacerbations was observed in Study 575 in OCS-dependent patients while reducing background OCS dose. Patients treated with mepolizumab 100 mg SC had a 32% reduction in rate of exacerbations (Rate ratio 0.68, 95% CI: 0.47,

0.99) compared with patients receiving placebo (p=0.042). While there was no exacerbation history requirement for inclusion in this study, 84% of patients had at least one exacerbation (mean 3.1 exacerbations) in the previous 12 months prior to the study and up to 67% had two or more exacerbations, demonstrating that despite use of maximum asthma therapy (including systemic corticosteroids), this population was not well controlled. Although numbers were small, fewer patients treated with mepolizumab experienced exacerbations requiring hospitalization or an ED visit (3 vs. 7), and exacerbations requiring hospitalization (0 vs. 7) compared with placebo.

4.4.4.2. Quality of Life

4.4.4.2.1. St. George's Respiratory Questionnaire (SGRQ)

At Week 24 when optimized OCS reduction occurred in Study 575, patients treated with mepolizumab had a statistically significant improvement in SGRQ score compared with placebo: -5.8 (95% CI: -10.6, -1.0; p=0.019). The treatment difference exceeded the MCID of -4.0 for this instrument. These results are similar to those observed in the Exacerbation Study 588.

4.4.4.2.2. Response to Therapy Assessment

In Study 575, similar to the Exacerbation Studies, Patient-Rated Response to Therapy at Week 24 showed a clear benefit in patients treated with mepolizumab. The odds ratio (OR) of being in a better response category was 2.73 (95% CI: 1.47, 5.07; p=0.002) in patients receiving mepolizumab 100 mg SC. Similarly, Clinician-Rated Response to Therapy showed an OR of 3.05 (95% CI: 1.63, 5.70; p<0.001) for patients receiving mepolizumab 100 mg SC.

4.4.4.3. Asthma Control

At baseline, ACQ-5 scores were >1.5, indicating poor asthma control even through patients were receiving optimized standard of care. At Week 24, after achieving maximal OCS reduction, patients treated with mepolizumab 100 mg SC reported a greater improvement from baseline compared with placebo in ACQ-5 score; the treatment difference of -0.52 points (95% CI: -0.87, -0.17) was statistically significant (p=0.004) and exceeded the MCID of 0.5.

4.4.4.4. Lung Function

4.4.4.4.1. FEV_1

Similar to Study 588, improvements in FEV_1 were observed with mepolizumab 100 mg SC compared with placebo during the course of Study 575. At the end of the 24-week treatment period when patients had achieved an optimal OCS reduction, the treatment difference in pre- and post-bronchodilator FEV_1 between mepolizumab and placebo was 114 mL (95% CI: -42, 271; p=0.151) and 128 mL (95% CI: -8 to 264 mL; p=0.064), respectively.

4.4.4.4.2. Peak Expiratory Flow

In Study 575, consistent improvements from baseline in morning PEF were also observed with mepolizumab, further supporting improved lung function. Treatment with mepolizumab 100 mg SC resulted in increases of 14.0 to 20.4 L/min vs. -2.5 to 4.1 L/min with placebo. The improvement in PEF observed with mepolizumab is similar to previously reported changes considered clinically relevant [Santanello, 1999].
A statistical comparison of mepolizumab vs. placebo was not pre-planned for this endpoint.

4.4.4.5. Eosinophils

Similar to the Exacerbation Studies, treatment with mepolizumab 100 mg SC in Study 575 resulted in rapid reduction of blood eosinophils (82% by the first assessment at Week 4; from mean counts of 230-250 cells/μL to 40 cells/μL) which was sustained over the duration of treatment.

4.5. Open-label Extension Studies 666 and 661

The eosinophil data presented for the OLE studies are from the interim analysis included in the BLA (data cut-off date February 28, 2014). These data support the durability of pharmacodynamic effect with mepolizumab.

4.5.1. Patient Disposition

A total of 998 patients from the Exacerbation Studies 997 and 588 and the OCS Reduction Study 575 have been enrolled in the OLE Studies (Table 17). More than half of patients who participated in Study 997 (347/616, 56%) enrolled in Study 666. There was ≥12 month treatment break between the two studies. Most patients who completed either Study 588 (522/539, 91%) or Study 575 (126/135, 93%) elected to continue treatment and directly rolled over into Study 661. All patients received mepolizumab 100 mg SC in the OLE Studies regardless of their treatment assignment in the double-blind parent study. Study 666 started before Study 661, thus patients have longer treatment exposure in this study. As of the February 28, 2014 data cut-off date for the interim analysis, 96% of patients were continuing treatment and there were 643 patient-years of exposure. The most common reasons for premature withdrawal from the OLE Studies were adverse event and withdrawal of consent (1% each).

Table 17 Patient Disposition and Exposure (OLE Studies, Interim Analysis)

	Study 661	Study 666	Total
Enrolled	651	347	998
Continuing treatment	633 (97)	325 (94)	958 (96)
Withdrawn	18 (3)	22 (6)	40 (4)
Primary reason for withdrawal			
Adverse event	6 (<1)	8 (2)	14 (1)
Withdrew consent	3 (<1)	8 (2)	11 (1)
Lack of efficacy	4 (<1)	0	4 (<1)
Protocol deviation	2 (<1)	2 (<1)	4 (<1)
Physician decision	3 (<1)	1 (<1)	4 (<1)
Lost to follow-up	0	2 (<1)	2 (<1)
Met protocol stopping criteria	0	1 (<1)	1 (<1)
Patient-years exposure	284	359	643

4.5.2. Eosinophils

Since mepolizumab treatment was restarted in Study 666 after a ≥12 month treatment break, blood eosinophil measurements during treatment showed a decrease of approximately 80% at all time points through Week 72 of the interim analysis. The mean screening blood eosinophil measurement, which was used as the baseline, was 240 cells/µL and on-treatment measurements averaged 45 cells/µL.

In Study 661, patients previously treated with mepolizumab in parent Studies 588 or 575 continued to show reduced eosinophil levels (50 to 60 cells/µL) through the data cut-off date (last measurement at Week 28), indicating a long-term sustained pharmacodynamic effect.

5. IDENTIFICATION OF CLINICAL AND BLOOD BIOMARKERS

5.1. Clinically Important Reduction in Risk of Exacerbations

Frequent and unpredictable exacerbations, requiring systemic corticosteroids and which may also require urgent care or even hospitalization, often dominate the expression of disease in patients with severe uncontrolled asthma. A key goal of the mepolizumab program was to develop a biomarker that helps to identify a patient likely to achieve a meaningful reduction in exacerbations with mepolizumab treatment. Asthma management guidelines do not define a lower threshold for the change in rate reduction or relative risk that is clinically meaningful; however, published studies provide important precedent.

Patients with increasing asthma severity receive intensive therapy following the evidence based step-wise treatment algorithm shown in Figure 2. Within this algorithm, ICS represent the cornerstone of treatment for all patients with moderate-to-severe asthma. Combination therapy of ICS + LABA has become established as the most effective

maintenance treatment for patients with moderate-to-severe asthma. The exacerbation reduction benefit of adding a LABA to ICS underpins the expert panel advice that ICS + LABA is the preferred treatment modality for patients with moderate-to-severe asthma who cannot be controlled with ICS alone. The exacerbation reduction benefit of LABA added to ICS was systematically reviewed by the independent Cochrane Airways Group [Gibson, 2007]. This meta-analysis examined 20 studies and 4312 patients who received ICS vs. ICS + LABA (similar ICS comparison) and also higher dose ICS vs. ICS + LABA (higher ICS comparison). A significant exacerbation risk reduction of 20% (0.80; 95% CI 0.73-0.89) was associated with the addition of LABA to ICS (similar ICS comparison). Similarly, a non-significant exacerbation risk reduction of 12% (0.88; 95% CI: 0.76-1.01) was associated with addition of LABA to higher doses of ICS (higher ICS comparison). Based on systematic review, the data supports that a 20% reduction in the risk of exacerbations is clinically relevant.

More relevant to mepolizumab is understanding the exacerbation reduction benefit associated with a biologic in patients already receiving maximal treatment with high-dose ICS+LABA (or other controllers). In this scenario, the only approved biologic for the treatment of asthma is omalizumab. The 28 week INNOVATE study included 419 patients inadequately controlled on high dose ICS + LABA [Humbert, 2005]. The study reported a significant and clinically meaningful 26% reduction (Rate ratio [RR] = 0.74; 95% CI: 0.552-0.998) in the rate of exacerbations (defined as worsening of asthma symptoms requiring treatment with systemic corticosteroids). This study was followed by a year-long study of 427 patients inadequately controlled on high dose ICS + LABA [Hanania, 2011]. This second study reported a significant and clinically meaningful 25% reduction (RR = 0.75; 95% CI: 0.61-0.92) in the rate of exacerbations (defined as worsening of asthma symptoms requiring treatment with systemic corticosteroids for 3 or more days; for patients receiving long-term OCS, an exacerbation was a 20 mg or more increase in the average daily dose of prednisone (or a comparable dose of another systemic corticosteroid). These studies provide precedents that a mean reduction in the exacerbation rate at the population level of at least 25% would be expected from future biologics intended to treat patients not well-controlled on high dose ICS + LABA (or other controller).

Based on these precedents, a reduction in the rate of exacerbations of 30% or more is considered to represent clinically meaningful benefit in patients with severe asthma who are uncontrolled on maximal standard of care therapy. Treatment with mepolizumab has been shown to be associated with a 50% reduction in exacerbations (those requiring systemic steroids), with a similar reduction in risk for the more severe exacerbations requiring ED visit or hospitalization. Recognizing that severe asthma is a heterogeneous disease and that the benefit provided by mepolizumab may be a continuum based on disease severity, eosinophil blood counts, or other factors, a meaningful 30% benefit threshold is reached even for patients at the lower end of the eosinophil biomarker criteria. The application of this concept is shown in Figure 19.

5.2. Selection of Patients Likely to Benefit from Treatment with Mepolizumab

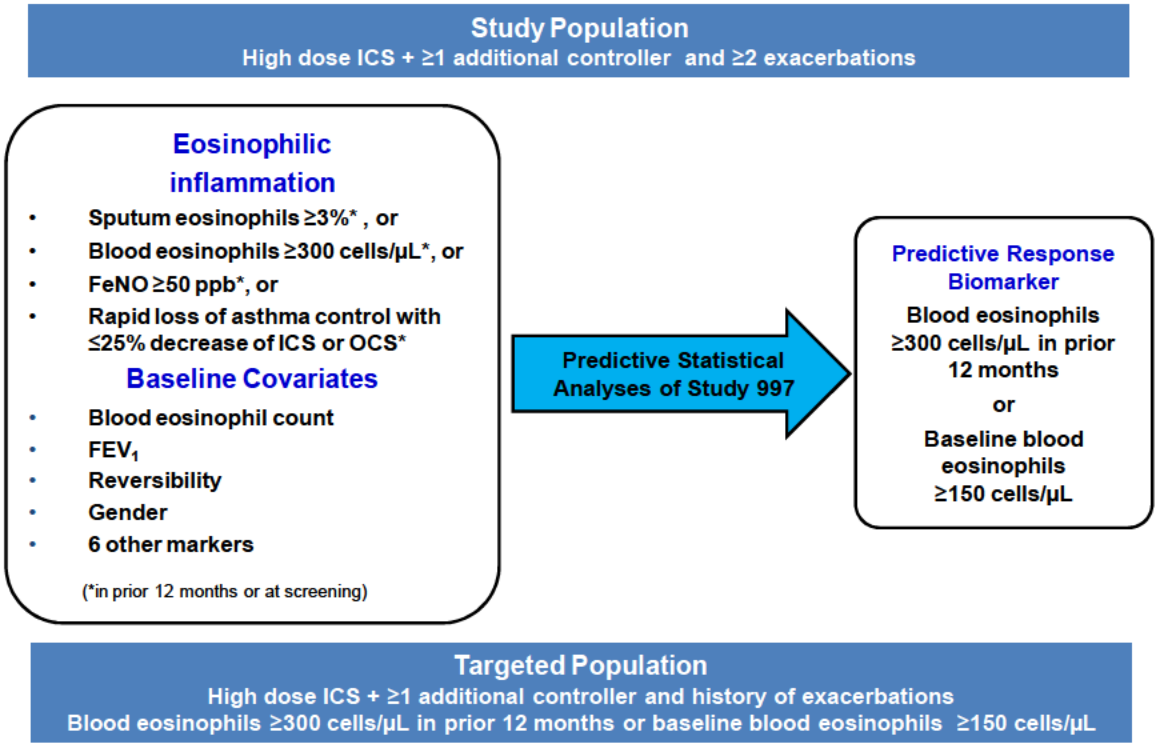
The proposed patient population for mepolizumab is based on key learnings from studies in the clinical development program.

Proof-of-Concept Studies 184 and 046 showed that mepolizumab should be used as an add-on treatment for patients with severe eosinophilic asthma, and that mepolizumab could reduce exacerbations and decrease use of maintenance OCS in this population. As an-add on therapy, it is important to first try to control asthma by maximizing the dose of ICS. Thus, all patients in the mepolizumab studies required high dose ICS plus at least one additional controller. For Study 184, all patients experienced 2 or more exacerbations in the prior year. These two clinical criteria were then used to define the patient population for future mepolizumab exacerbation studies (Figure 18).

Based on the positive results of Studies 184 and 046, Study 997 was conducted to evaluate the efficacy and safety of 75, 250, and 750 mg IV doses of mepolizumab compared with placebo on top of standard of care for 52 weeks. Both Proof-of-Concept studies were conducted at specialized centers and evidence of eosinophilic inflammation was documented through collection of induced sputum, a procedure performed at these centers. Since collection of sputum eosinophils is difficult and not routinely performed in clinical practice, Study 997 used an expanded set of four criteria to identify the presence of eosinophilic inflammation (see Section 3.2.2.1 and Figure 18).

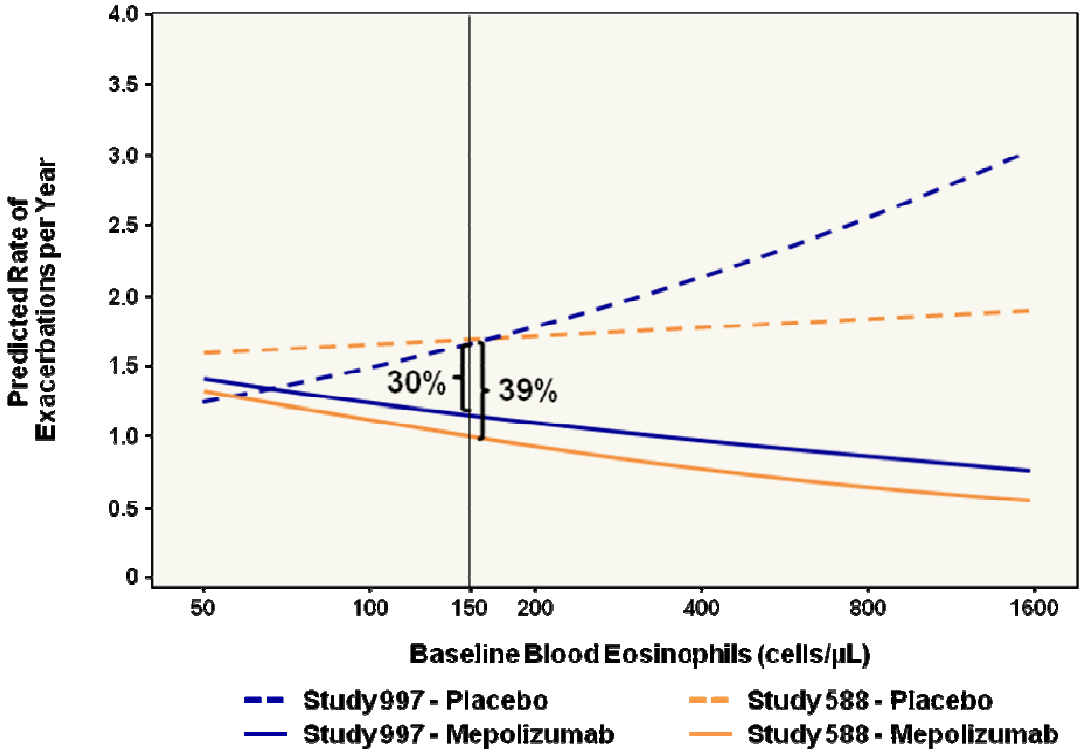
Study 997 confirmed that mepolizumab produced clinically important reductions in exacerbations (Section 4.3.3). Further modeling and subgroup analyses were performed in order to understand the groups of patients for which mepolizumab was most effective in reducing exacerbations. Modeling analyses investigated various clinical characteristics as individual covariates in Study 997 (i.e., gender, age, weight, geographical region, baseline FEV_1, reversibility at screening, number of exacerbations in previous year, baseline blood eosinophil count, baseline use of maintenance OCS, and IgE level) to distinguish which variables would best predict a reduction in the rate of exacerbations (Figure 18). The model identified blood eosinophils as the strongest predictor of treatment response.

Figure 18 Biomarker Identification from Study 997



Modeling analysis investigating clinical characteristics predictive of response was repeated for Study 588. Predicted exacerbation rates for Studies 997 and 588 as a function of baseline blood eosinophil counts are shown in Figure 19. The lines depicting the predicted exacerbation rates for patients receiving mepolizumab and those receiving placebo diverge with increasing baseline blood eosinophil values. In other words, there is a direct relationship between baseline eosinophil count and the predicted reduction in exacerbation rate. At 150 cells/µL, the reduction in exacerbation rate is estimated to be 30% and 39%, in Studies 997 and 588 respectively, both representing clinically meaningful reductions in exacerbation rate as discussed above in Section 5.1. Thus, while both studies showed a reduction in rate of exacerbations of approximately 50% in the overall population, in the patients with the lowest eosinophil baseline counts for eligibility for treatment with mepolizumab, a clinically important 30% or greater reduction in exacerbation risk would be predicted based on these data.

Figure 19 Modeling Analysis: Predicted Rate of Exacerbations by Baseline Blood Eosinophil Count (Studies 997 and 588)



In addition, subgroup analyses of Study 997 showed that among patients with blood eosinophil counts of <150 cells/µL, patients with a history of blood eosinophil level of ≥300 cells/µL also derived benefit from mepolizumab compared with placebo, with a 33% reduction in exacerbation risk. This observation formed the basis of the inclusion criteria for Study 588 (see Section 5.2.1) and the recommended population to be treated with mepolizumab.

Subgroup analysis also investigated whether presence of sputum eosinophilia would predict greater response with mepolizumab. Sputum eosinophils were collected at baseline in a substudy of 94 patients. In this sub-study, sputum eosinophils did not predict treatment response, with an approximately 70% reduction in exacerbations occurred in both the high sputum eosinophilia group (>3%) and the low sputum eosinophilia group (3%) [Katz, 2013].

5.2.1. Subgroup Analyses of Exacerbations Based on Eosinophil Thresholds

To examine the comparative predictive nature of the biomarker, exacerbation rates from Studies 997 and 588 were analyzed by each separate eosinophil enrollment criterion (Table 18). Patients who did not meet either eosinophil criterion showed little clinical benefit with mepolizumab (10% exacerbation reduction). Patients who met the baseline criterion and patients who met the historical criterion both showed a similar exacerbation

benefit (approximately 50% reduction), which is clinically relevant in this severe population. Thus, either criterion is predictive of response.

Table 18 Exacerbation Reduction Stratified by Categories of Blood Eosinophil Criteria (Studies 997 and 588, ITT Population)

Biomarker Thresholds Blood Eosinophils (cells/μL)		Study 997 N=616		Study 588 N=576	
		n	% Reduction	n	% Reduction
Did not meet baseline or historical		94	10%	---	N/A[1]
Baseline	≥150 cells/μL at treatment start	467	54%	453	53%
Historical	≥300 cells/μL in previous 12 months	365	51%	496	49%

1. All patients in Study 588 were required to meet either the baseline or the historical criteria.
Note: Some patients met both criteria

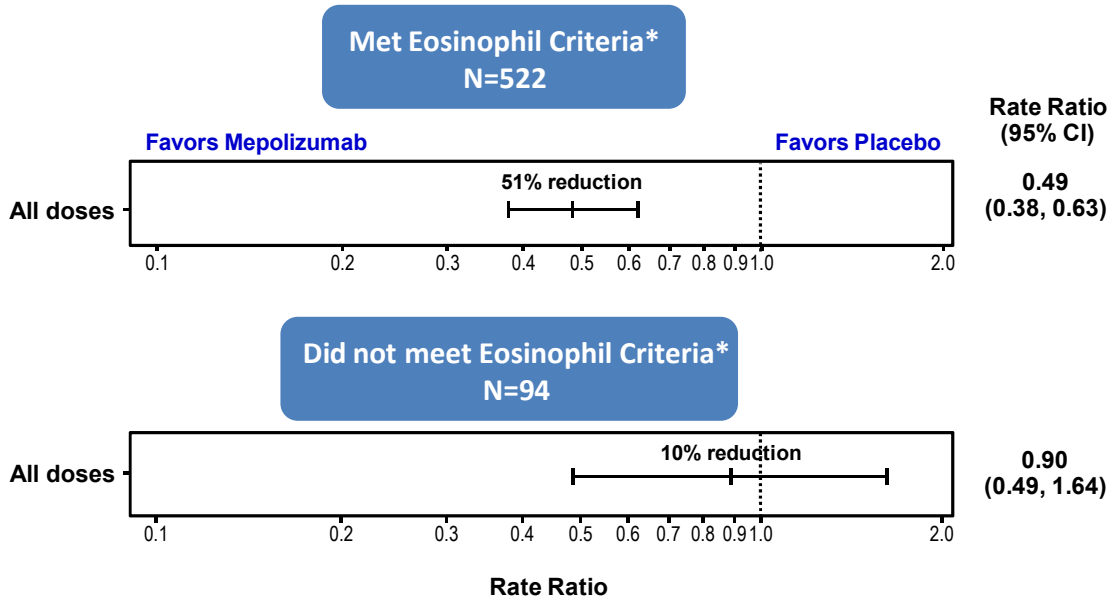
Further analysis was also performed to examine the reduction in exacerbations for patients who met only one of the two eosinophil criteria (Table 19). Clinically relevant reductions in exacerbations were observed for both groups of patients indicating that both criteria contribute to the identification of patients who would benefit from treatment with mepolizumab. It should be noted only 13% of the total ITT Population met the historical eosinophil criterion only.

Table 19 Exacerbation Reduction for Patients Meeting Only One of the Blood Eosinophil Criteria (Studies 997 and 588, ITT Population)

	Blood Eosinophils (cells/μL)	n	Rate Ratio Mepolizumab/Placebo (95% CI)	% Reduction in Exacerbations
Baseline only	≥150 cells/μL at treatment start No evidence of ≥300 cells/μL in previous 12 months	215	0.44 (0.29, 0.67)	56%
Historical only	<150 cells/μL at treatment start Evidence of ≥300 cells/μL in previous 12 months	149	0.67 (0.42, 1.08)	33%

In addition, because of the different entry criteria for Study 997 and Study 588, a post-hoc analysis of the primary endpoint for Study 997 was conducted using the eosinophil criteria used in Study 588 (≥150 cells/μL at baseline or ≥300 cells/μL within the previous 12 months; the refined target population for mepolizumab treatment). This analysis showed that patients treated with mepolizumab who met the eosinophil criteria had a 50% reduction in the rate of exacerbations over placebo compared with a 10% reduction in patients who did not meet the eosinophil criteria (Figure 20). These results support the utility of the biomarker criteria to identify a patient likely to benefit from treatment with mepolizumab.

Figure 20 Exacerbation Response Stratified by Eosinophil Criteria defined in Study 588* (Study 997)



* Blood eosinophils ≥150 cells/µL at baseline or ≥300 cells/µL in last 12 months

5.2.2. Summary of Blood Eosinophil Biomarker and Evidence of Durability of Single Baseline Measurement

Blood eosinophil count is a biomarker easily accessible to health care providers. It is also inexpensive and the results can be available in a relatively short period of time after collection. Taking into account that patients treated with high doses of ICS (and OCS) may have reduced eosinophil levels, from the model developed (Figure 19), the threshold of 150 cells/µL provides a reliable means to identify the patient population with severe asthma that is likely to benefit from mepolizumab treatment. Additionally, historical levels (≥300 cells/µL) allow flexibility to start a patient with severe asthma immediately on treatment if deemed appropriate by the health care provider. The clinical utility of the eosinophil threshold criteria were confirmed in Studies 588 and 575 as discussed above.

The utility of a single blood measure, and whether using the average of repeated consecutive eosinophil measurements to produce a more accurate prediction of the future eosinophil level, was assessed. An analysis in patients receiving placebo from Study 997 showed that a single measurement of blood eosinophils ≥150 cells/µL at screening was predictive of the average of subsequent measurements remaining ≥150 cells/µL in 85% of patients studied [Katz, 2014]. Using an average of multiple measurements only marginally increased the sensitivity, providing support that a single measurement is sufficient in most of the cases.

6. SAFETY RESULTS

6.1. Overview

Key Findings:

In patients with severe eosinophilic asthma, the safety profile of mepolizumab plus standard of care was similar to placebo plus standard of care. The safety profile of mepolizumab 100 mg SC was similar to the integrated safety profile observed across a 10-fold dose range (75 mg to 750 mg IV). To date, no serious risks clearly attributable to mepolizumab or predisposing factors for AEs have been identified.

In the Randomized Controlled (RCT) Studies 997, 588 and 575:

- There have been no reports of anaphylaxis associated with mepolizumab treatment.
- Mepolizumab was not associated with increased risk of overall systemic reactions (including hypersensitivity reactions), infections (including serious infections or opportunistic infections), neoplasm or malignancy, or cardiac/vascular/ thromboembolic events.
- Based on both the low incidence (6% 100 mg SC and 2% all IV doses) and low titer of ADA and neutralizing antibodies, the immunogenicity data demonstrated a low risk for loss of efficacy, ADA-associated AEs, and/or altered PK/PD.
- The overall incidence of AEs was similar between placebo (82%) and mepolizumab (79% 100 mg SC and 83% 75 mg IV). The most frequently reported AEs were headache and nasopharyngitis.
- The incidence of SAEs and withdrawals due to AEs was lower for mepolizumab 100 mg SC (6% and 1%, respectively) and 75 mg IV (10% and 1%, respectively) compared with placebo (15% and 3%, respectively).
- No treatment related effects on clinical laboratory tests, vital signs, or electrocardiograms (ECGs) were evident.
- No reports of rebound of disease or other AEs indicative of worsening of disease have been reported following cessation of mepolizumab treatment.

In the Open-Label Extension (OLE) Studies, the long-term safety profile of mepolizumab was similar to the RCT Studies including the safety profile observed with restart of mepolizumab treatment in Study 666 after an off treatment period ranging from 12 to 18 months.

6.2. Introduction

For the assessment of mepolizumab safety in the severe eosinophilic asthma development program, integrated data are presented for two sets of studies:

- Randomized Controlled (**RCT**) Studies: Exacerbation Studies 997 and 588, and OCS Reduction Study 575
- Open-label Extension (**OLE**) Studies: Studies 661 and 666

Safety analyses were performed on the Safety Population defined as all patients who received at least one dose of study medication.

Study 997 examined doses of 75, 250 and 750 mg IV and the safety profile showed no differentiation across this 10-fold dose range. The focus of the discussion for safety are results for the 100 mg SC dose proposed for marketing and the corresponding equivalent 75 mg IV dose (see Section 4.2 for additional information); however, an All Doses (75, 250, 750 mg IV, and 100 mg SC combined) column is shown in the tables for completeness.

The safety data presented for the OLE studies is from the interim analyses (data cut-off date February 28, 2014) submitted in the BLA unless otherwise indicated.

6.3. Extent of Exposure

Over 2000 patients have participated in the asthma clinical development program; of these, 1596 patients have been exposed to mepolizumab. A total of 1327 patients with severe eosinophilic asthma have been enrolled to date and 1229 of these patients have received mepolizumab. Of these 1229 patients, 1018 (83%) have received mepolizumab 100 mg SC and 442 patients (43%) have been exposed to this dose for at least 12 months (Table 20).

Table 20 Extent of Exposure in Mepolizumab Asthma Studies

Studies	Placebo	Mepolizumab				
		100mg SC	75mg IV	250mg IV	750mg IV	All Doses
Number of Patients, n						
All Asthma Studies[1]	581	1018	355	275	285	1596
RCT + OLE Studies[2]	412	1018	344	152	156	1229
RCT Studies	412	263	344	152	156	915
Patient-Years						
RCT + OLE Studies[2]	284	789	254	142	144	1329
RCT Studies	284	147	254	142	144	687
Length of Exposure RCT + OLE Studies[2], n (%)						
1 to <3 months	8 (2)	35 (3)	10 (3)	4 (3)	4 (3)	40 (3)
3 to <6 months	32 (8)	221 (22)	18 (5)	8 (5)	10 (6)	152 (12)
6 to <12 months	248 (60)	320 (31)	189 (55)	10 (7)	12 (8)	292 (24)
12 to <24 months	124 (30)	442 (43)	127 (37)	130 (86)	130 (83)	526 (43)

1. GSK-sponsored studies: 4 clinical pharmacology studies and Phase II/III studies 006, 092, 997, 588, 575, 666, and 661
2. Randomized Controlled Studies include 997, 588, and 575; Open-label Extension Studies include 666 and 661

Note: A patient who participated in more than one study (i.e., RCT study and an OLE extension study) and received different doses is counted once in each dose and once in the "All Doses" column.

As of the data cut-off date for the 120 Day Safety Update (October 27, 2014), total exposure to mepolizumab 100 mg SC in the OLE Studies was 1180.63 patient-years. The majority of patients (83%) have been treated with mepolizumab 100 mg SC from 12 to <24 months. Patients who received mepolizumab 100 mg SC in the RCT Studies 588 or 575, or in the OLE Studies 666 and 661, (N=1018) have received 1327.00 patient-years of exposure to mepolizumab. As of October 27, 2014, the total exposure to mepolizumab in the severe asthma studies, regardless of dose or route, was 1866.22 patient-years or a median of 18.2 months.

6.4. Adverse Events of Special Interest

AEs of special interest were prospectively identified in the severe eosinophilic asthma program. These are events considered potentially associated with mepolizumab treatment based on its pharmacologic properties and mechanism of action. IV and/or SC administration of a monoclonal antibody could be associated with systemic (allergic/hypersensitivity and non-allergic) reactions, local site reactions due to SC administration, or development of anti-drug antibodies. Since treatment with mepolizumab results in a decrease in eosinophils, which is a component of innate immunity, both infections and malignancies were identified as events of special interest. Since patients in this program were taking high dose ICS, opportunistic infections were also examined. Cardiovascular (CV) events were included as an AE of special interest since the severe eosinophilic asthma population tends to be older with increased CV risk factors and because mepolizumab is a first in class medication.

6.4.1. Systemic (Allergic/Hypersensitivity and Non-allergic) Reactions

Hypersensitivity/anaphylaxis is a potential risk of concern with biologics, and as such, a diligent effort was undertaken during the severe asthma clinical program to monitor, record, and assess all systemic reactions. When a systemic reaction was reported, investigators were asked to make a determination if the reaction was allergic (i.e., hypersensitivity) or non-allergic (e.g., anaphylactoid or those due to cytokine release) to assist with decision-making regarding continued treatment with mepolizumab and/or the need for administration of prophylactic medications such as antihistamines prior to subsequent dosing. Investigators were required to complete an additional assessment of all systemic reactions against the standard diagnostic criteria for anaphylaxis as outlined by the 2006 Joint National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network (NIAID/FAAN) [Sampson, 2006].

RCT Studies

The overall incidence of systemic reactions was similar between placebo (5%) and all doses of mepolizumab (6%). Systemic allergic/hypersensitivity reactions were reported by ≤2% of patients and rates were similar across the placebo and mepolizumab 100 mg SC and 75 mg IV groups (Table 21). Non-allergic reactions were reported by 2% of patients in the mepolizumab 100 mg SC group and 3% of patients in the placebo and mepolizumab 75 mg IV groups.

There were no reports from investigators of anaphylaxis considered possibly related to treatment with mepolizumab in any severe eosinophilic asthma studies. A standard

Medical Dictionary for Regulatory Activities (MedDRA) query (SMQ) for anaphylactic reactions was retrospectively conducted to identify any suspected reactions that may have been inadvertently unidentified by the investigators. No suspected reactions were noted.

Table 21 Systemic Reactions (RCT Studies, Safety Population)

Systemic Reactions	Number (%) of Patients			
		Mepolizumab		
	Placebo N=412	100 mg SC N=263	75 mg IV N=344	All Doses N=915
Any Event	20 (5)	7 (3)	12 (3)	54 (6)
Hypersensitivity (allergic)	7 (2)	3 (1)	4 (1)	12 (1)
Anaphylaxis	0	0	0	0
Non-allergic reactions	14 (3)	4 (2)	9 (3)	44 (5)

Furthermore, a retrospective review of AEs associated with eczema/rash, dyspnea and nasal congestion events was undertaken to determine if the increased reporting of these AEs compared with placebo was associated with unrecognized hypersensitivity or anaphylactoid events. Upon review of associated AEs experienced by 182 patients with at least one of these events, no cases were identified that had associated AEs suggestive of hypersensitivity or anaphylactoid reactions.

Almost all systemic reactions occurred on the day of dosing. The most common symptoms reported with any systemic reaction included headache, rash, pruritus, fatigue, and dizziness.

OLE Studies

A similar incidence of systemic hypersensitivity reactions and non-allergic reactions were reported in the OLE studies (<1% in each study). Restart of mepolizumab in Study 666 after ≥12 month treatment break from Study 997 had no effect on the incidence or type of these reactions.

All systemic reactions reported in the severe eosinophilic clinical program to date have been non-serious with the exception one. A serious Type IV delayed hypersensitivity reaction with an onset 3 days after administration of the 9th monthly dose of mepolizumab 100 mg SC was reported (Study 661), which resolved following hospitalization in the ICU and treatment with adrenaline.

6.4.2. Local Injection Site Reactions

RCT Studies

In the placebo-controlled Severe Asthma Studies, local injection site reactions were reported for more patients treated with mepolizumab 100 mg SC (21 patients, 8%) compared with the mepolizumab 75 mg IV (11 patients, 3%) and placebo (14 patients, 3%). All local site reactions have been non-serious, were of mild or moderate intensity (i.e., severity), and resolved within a few days. Pain, erythema, swelling, itching, and burning sensation were the most common symptoms reported.

OLE Studies

In the OLE Studies, a similar low incidence of injection site reactions to the RCT Studies has been observed: 5% overall; 9% in Study 666 and 4% in Study 661.

6.4.3. Immunogenicity

All therapeutic proteins have the potential to induce an ADA response in a patient; ADAs may alter PK, PD, or produce adverse reactions, however, in most circumstances, ADAs are of no clinical significance. Humanized monoclonal antibodies inherently have a low immunogenicity potential since the antibody protein sequence is homologous as if produced by the host, and thus has a low probability to be recognized as a foreign protein.

The immunogenicity sampling strategies for the Phase III program were similar with the exception of the inclusion of a post-study immunogenicity sample obtained 24 weeks after the last dose. All three RCT Studies included a baseline sample, one at Week 16, and one at study end. The 24 week post-last dose sample was included in Study 997 to assure >99% washout of mepolizumab, including the 750 mg IV arm, thereby greatly minimizing false positive samples due to mepolizumab interference or mepolizumab-IL5 complex interference.

Overall, based on results to date, mepolizumab has low immunogenic potential and ADA formation is not expected to impact the overall clinical benefit of mepolizumab treatment.

RCT Studies

In the RCT Studies, 15 patients (6%) treated with 100 mg SC and 10 patients (3%) treated with 75 mg IV mepolizumab had anti-mepolizumab antibodies after having received at least one dose (Table 22). Antibody titers were low and mostly transient; 50% of these patients had only one positive test result.

Table 22 Immunogenicity Results (RCT Studies, Safety Population)

	Number (%) of Patients			
		Mepolizumab		
Immunogenicity Results	Placebo N=412	100 mg SC N=263	75 mg IV N=344	All Doses N=915
ADA Assay				
Positive	5 (1)	15 (6)	10 (3)	28 (3)
Median titer value (Min, Max)	8 (4, 32)	32 (6, 640)	24 (4, 128)	32 (2, 640)
NAb Assay				
Positive	0	1 (<1)	0	1 (<1)

ADA = Anti-drug Antibody
NAb = Neutralizing Antibodies

The profile of AEs was similar for ADA positive and negative patients and frequencies were not higher in ADA positive patients across any SOCs. In patients that had high titers, no AEs related to potential systemic allergic reactions or any pattern of worsening injection site reactions was observed.

One patient who received 100 mg SC developed neutralizing antibodies to mepolizumab following the second injection. The patient experienced moderate injection site reaction with symptoms of erythema and itching 6 days after the first injection. The event was considered non-serious by the investigator. Bronchitis, eczema, and sinus tachycardia were also reported as AEs during the same timeframe as the reaction. The injection site reaction led to withdrawal from the study and resolved 60 days later.

Across the Phase III program, anti-mepolizumab antibodies did not discernibly impact the PK or PD of mepolizumab treatment in the majority of patients and there was no correlation between antibody titers and change in blood eosinophil count. AEs evaluated as potential systemic allergic reactions were uncommon (≤2%) and not related to study drug in ADA-positive patients. There were no signals for serious acute hypersensitivity reactions or serum sickness-like reactions associated with positive anti-mepolizumab antibody status.

OLE Studies

In the OLE Studies 666 and 661, the immunogenicity incidence rate (5% each study), including antibody characteristics, appears similar to the RCT studies. Reintroduction of mepolizumab in Study 666 following treatment cessation of ≥12 months since Study 997 did not have a significant impact on immunogenicity results.

6.4.4. Infections

Eosinophils are a component of innate immunity but are not directly involved in adaptive immune responses. As mepolizumab only binds to IL-5, it should not impact T cell or B cell function. Both preclinical and clinical evidence to date are not suggestive of an increased risk of infections associated with mepolizumab.

Because patients with severe eosinophilic asthma are also taking high-dose corticosteroids, the incidence of opportunistic infections was also examined.

Literature suggests that IL-5 antagonism may alter the kinetics of clearance for helminth infection, but does not prevent clearance or increase the chances of initial infection [Kopf, 1996; Tanaka, 2000]. Because there is not complete depletion of circulating eosinophils during mepolizumab treatment, persisting eosinophils may provide an appropriate physiologic immune response, minimizing the risk and response to treatment of parasitic infections. Patients with known parasitic infections were excluded from participation. The clinical trials were not designed to study the effect of mepolizumab on risk for, or response to treatment for, helminth infections. However, it is recommended that pre-existing helminth infections are treated prior to starting mepolizumab.

The helminth infection rate in the overall global clinical program (all indications) was less than 1 in 1000 patients.

RCT Studies

In the RCT Studies, infections, including serious and opportunistic, were reported at a similar incidence in the placebo group and the mepolizumab groups (Table 23). The

most frequent infection AEs (reported at an incidence of ≥10% in at least one treatment group) were nasopharyngitis, upper respiratory tract infection (URTI), and sinusitis, which are commonly reported in asthma studies.

Pneumonia-related events were the most frequent infection SAE and occurred in <1% of patients in the placebo and mepolizumab groups; all events were non-fatal. Bronchitis, herpes zoster, and viral URTI were other non-fatal SAEs reported for more than one patient. One patient experienced an infection with a fatal outcome. A 60-year old female patient receiving mepolizumab 250 mg IV experienced biliary microlithiasis which resulted in severe acute pancreatitis and distributive septic shock (see Section 6.8).

Opportunistic infections (primarily herpes zoster involving multiple dermatomes) were infrequent and were reported in ≤1% of patients in both the mepolizumab and placebo groups.

Table 23 Infections and Infestations (RCT Studies, Safety Population)

	Number (%) of Patients			
		Mepolizumab		
Infections and Infestations	Placebo N=412	100 mg SC N=263	75 mg IV N=344	All Doses N=915
Any event	239 (58)	136 (52)	209 (61)	519 (57)
Most common (≥10%) events				
Nasopharyngitis	80 (19)	43 (16)	79 (23)	184 (20)
URTI	47 (11)	27 (10)	32 (9)	96 (10)
Sinusitis	40 (10)	24 (10)	21 (6)	68 (7)
Any SAE	14 (3)	7 (3)	8 (2)	23 (3)
Fatal SAEs	0	0	0	1 (<1)
Non-fatal SAEs in >1 patient				
Pneumonia-related	4 (<1)	1 (<1)	3 (<1)	7 (<1)
Bronchitis	2 (<1)	0	1 (<1)	1 (<1)
Herpes zoster	0	2 (<1)	0	2 (<1)
Viral URTI	1 (<1)	0	1 (<1)	1 (<1)
Opportunistic infections	4 (<1)	3 (1)	4 (1)	9 (<1)
Herpes zoster	2 (<1)	2 (<1)	4 (1)	6 (<1)
Blastomycosis	1 (<1)	0	0	0
Gastrointestinal fungal infection	0	1 (<1)	0	1 (<1)
Ophthalmic herpes simplex	1 (<1)	0	0	0
Ophthalmic herpes zoster	0	0	0	1 (<1)
Respiratory moniliasis	0	0	0	1 (<1)

UTRI = upper respiratory tract infection

OLE Studies

The profile of infections and infestations AEs in the OLE studies remained similar to the 100 mg SC dose in the RCT studies. The overall incidence was 55%; nasopharyngitis (23%) and URTI (10%) were reported most often. The incidence of infection SAEs was 2%, with pneumonia being reported most often (<1%). Opportunistic infections were reported for <1% of patients.

6.4.5. Neoplasms and Malignancies

The known biology of IL-5 and eosinophils suggest that blocking the binding of IL-5 to its receptor with mepolizumab would be unlikely to induce an immunosuppressive effect that would impair host surveillance against malignancy. Both preclinical and clinical evidence to date are not suggestive of an increased risk of malignancies associated with mepolizumab.

RCT Studies

In the RCT Studies, neoplasms (both benign and malignant) were infrequent and occurred at a similar frequency across all treatment groups (Table 24). The types of malignancies reported were those that are common in the general population. None of the types of malignancies were reported in more than one patient in the RCT Studies. There was no evidence of an increased probability of occurrence with increased exposure to mepolizumab treatments compared with placebo. Across the asthma program, there have been no reports of lymphoma or other lymphoproliferative cancers suggestive of a general immunosuppression.

Table 24 Neoplasms and Malignancies (RCT Studies, Safety Population)

	Number (%) of Patients			
		Mepolizumab		
Neoplasms and Malignancies	Placebo N=412	100 mg SC N=263	75 mg IV N=344	All Doses N=915
Neoplasms				
Any event	9 (2)	2 (<1)	4 (1)	7 (<1)
SAEs (non-fatal)	2 (<1)	0	0	1 (<1)
Malignancies				
Any event	3 (<1)	0	1 (<1)	2 (<1)
Basal cell carcinoma	0	0	1 (<1)	1 (<1)
Basosquamous carcinoma	1 (<1)	0	0	0
Squamous carcinoma	1 (<1)	0	0	0
Prostate cancer	1 (<1)	0	0	0
Uterine cancer	0	0	0	1 (<1)

OLE Studies

In the OLE studies, neoplasms (benign and malignant) were reported for 11 patients (1%). Malignancies were reported for 4 patients (<1%): breast cancer (2 patients), gastric cancer (1 patient), and prostate cancer (1 patient).

6.4.6. Cardiovascular Events

Cardiovascular safety is a key aspect of understanding risk associated with therapeutic agents, particularly in an older severe asthma population with an increased risk for cardiovascular comorbidities such as hypertension and diabetes mellitus. Based on the mechanism of action of mepolizumab, there is no plausible biologic reason for cardiac or vascular effects and no formal QTc study was required. Moreover, there was no evidence

of cardiac or vascular pathology in the safety assessment of mepolizumab in preclinical toxicology studies.

Nonclinical and clinical data from the overall program supports a low risk of CV toxicity. Mepolizumab is a large molecule, thus cardiotoxicity resulting from direct human ether-a-go-go related gene (hERG) channel blockade is generally not a concern and low risk for QT-mediated proarrhythmia. Prior to the Phase III severe asthma program, a cross-study analysis of all ECG data related to QTc interval data was performed and determined mepolizumab does not affect the QTc interval. Additionally, ECG monitoring in Phase III severe asthma program disclosed no treatment-related effects on QTc intervals or heart rate (see Section 6.12).

The integrated data from the RCT Studies showed that cardiac disorders (all events) were infrequent, 3% in both placebo and mepolizumab (all doses combined) groups. Serious cardiac, vascular, and thromboembolic (CVT) events were reported with similar frequency rates across all treatment groups including placebo (<1% to 1%) (Table 25).

Table 25 Overview of Cardiovascular Adverse Events (RCT Studies, Safety Population)

	Number (%) of Patients			
		Mepolizumab		
Cardiovascular Grouping	Placebo N=412	100 mg SC N=263	75 mg IV N=344	All Doses N=915
All AEs				
Cardiac SOC	12 (3)	6 (2)	8 (2)	26 (3)
Vascular SOC	23 (6)	9 (3)	17 (5)	44 (5)
Non-fatal SAEs				
Cardiac, Vascular, and Thromboembolic[1]	3 (<1)	1 (<1)	4 (1)	11 (1)
Cardiac SOC	1 (<1)	1 (<1)	2 (<1)	8 (<1)
Vascular SOC	0	0	2 (<1)	4 (<1)
Relevant AEs from other SOCs	2 (<1)	0	0	1 (<1)

1. In addition to the Cardiac and Vascular SOCs, relevant AEs from other SOCs (e.g., stroke from the Nervous system Disorders SOC) were included for comprehensive summary of all relevant SAEs of CVT nature

OLE Studies

Similar to the RCT Studies, CVTs have been reported for <1% of patients treated with 100 mg SC in the OLE studies.

6.5. Common Adverse Events

RCT Studies

In the RCT Studies, the overall incidence of AEs was similar between the placebo and mepolizumab groups (79% to 83%). The most frequently reported AEs were headache and nasopharyngitis which are common in an asthmatic population.

Generally, similar AE profiles were observed regardless of the route of mepolizumab administration (IV or SC) with the exception of a higher rate of injection site reactions with SC administration (see Section 6.4.2), which is expected. Events that were reported with an incidence of at least 5% in the mepolizumab 100 mg SC or 75 mg IV groups along with the corresponding exposure adjusted event rates are shown in Table 26.

Table 26 Adverse Events Reported in ≥5% of Patients in Either Mepolizumab 100 mg SC or 75 mg IV Treatment Group (RCT Studies, Safety Population)

Adverse Event (Preferred Term)	Number (%) of Patients			
		Mepolizumab		
	Placebo N=412	100 mg SC N=263	75 mg IV N=344	All Doses N=915
Any Event	338 (82)	209 (79)	287 (83)	742 (81)
Headache	74 (18)	53 (20)	78 (23)	195 (21)
Nasopharyngitis	80 (19)	43 (16)	79 (23)	184 (20)
Asthma	61 (15)	15 (6)	32 (9)	89 (10)
URTI	47 (11)	15 (6)	32 (9)	96 (10)
Bronchitis	39 (9)	16 (6)	31 (9)	73 (8)
Sinusitis	40 (10)	25 (10)	21 (6)	68 (7)
Back pain	20 (5)	16 (6)	22 (6)	60 (7)
Arthralgia	23 (6)	16 (6)	16 (5)	50 (5)
Oropharyngeal pain	27 (7)	11 (4)	16 (5)	45 (5)
Cough	21 (5)	5 (2)	16 (5)	41 (4)
Fatigue	17 (4)	12 (5)	14 (4)	35 (4)
Influenza	15 (4)	7 (3)	16 (5)	37 (4)
Pain in extremity	16 (4)	12 (5)	8 (2)	32 (3)
Injection site reaction[1]	14 (3)	21 (8)	11 (3)	32 (3)
Adverse Event (Preferred Term)	**Exposure Adjusted[1]**			
		Mepolizumab		
	Placebo Pt Yrs=284	100 mg SC Pt Yrs=147	75 mg IV Pt Yrs=254	All Doses Pt Yrs=687
Any Event	6161.6	7038.1	6009.9	5869.7
Headache	647.8	691.6	1321.5	853.9
Nasopharyngitis	355.6	420.4	409.0	384.0
Asthma	383.8	278.0	216.3	215.3
URTI	225.3	217.0	220.3	218.2
Bronchitis	154.9	128.8	157.3	138.2
Sinusitis	186.6	203.4	106.2	122.2
Back pain	102.1	122.0	106.2	100.4
Arthralgia	98.6	149.2	78.7	93.1
Oropharyngeal pain	116.2	88.1	102.3	90.2
Cough	81.0	33.9	70.8	69.8
Fatigue	81.0	169.5	78.7	78.6
Influenza	59.9	47.5	74.7	62.6
Pain in extremity	66.9	81.4	31.5	46.6
Injection site reaction[1]	105.6	284.8	55.1	81.5

1. Numbers represent the frequency of events per 1000 patient-years of exposure
2. Data for injection site reaction are from the targeted eCRF page which is a more conservative and solicited reporting approach

The most frequently reported AEs considered drug related by the investigators in the placebo and mepolizumab 100 mg SC and 75 mg IV groups were headache (2%, 5%, and 3%, respectively) and injection site reaction (3%, 6%, and 2%, respectively).

OLE Studies

With open-label mepolizumab treatment, the AE profile has remained similar to the RCT Studies. After restart of treatment following at least a 12 month treatment break, the AE profile in Study 666, including drug-related AEs, was also similar to the AE profile of the RCT Studies.

6.6. Non-fatal Serious Adverse Events

RCT Studies

Non-fatal SAEs occurred in a larger proportion of patients treated with placebo (15%) compared with mepolizumab 100 mg SC (6%) or 75 mg IV (10%); this difference was primarily due to a higher incidence of asthma exacerbation in patients receiving placebo (Table 27). The incidence of other SAEs in the mepolizumab groups was similar to or less than the placebo group for the majority of events.

The exposure-adjusted incidence of non-fatal SAEs in the mepolizumab 100 mg SC and 75 mg IV groups was less than the exposure adjusted incidence of SAEs in the placebo group.

Table 27 Non-fatal Serious Adverse Events Occurring in More than One Patient (RCT Studies, Safety Population)

Serious Adverse Event (Preferred Term)	Number (%) of Patients			
		Mepolizumab		
	Placebo N=412	100 mg SC N=263	75 mg IV N=344	All Doses N=915
Any SAE	63 (15)	17 (6)	34 (10)	92 (10)
Asthma	38 (9)	5 (2)	20 (6)	49 (5)
Pneumonia	3 (<1)	1 (<1)	1 (<1)	4 (<1)
Nephrolithiasis	3 (<1)	1 (<1)	0	1 (<1)
Bronchitis	2 (<1)	0	1 (<1)	1 (<1)
Lobar pneumonia	1 (<1)	0	2 (<1)	2 (<1)
Tendon rupture	1 (<1)	0	1 (<1)	2 (<1)
Atrial flutter	1 (<1)	1 (<1)	0	1 (<1)
Cerebrovascular accident	2 (<1)	0	0	0
Herpes zoster	0	2 (<1)	0	2 (<1)
Hypersensitivity	1 (<1)	1 (<1)	0	1 (<1)
Hypertension	0	0	1 (<1)	2 (<1)
Myocardial ischemia	0	0	1 (<1)	2 (<1)
Viral URTI[1]	1 (<1)	0	1 (<1)	1 (<1)
	Exposure Adjusted[2]			
	Placebo Pt Yrs=284	100 mg SC Pt Yrs=147	75 mg IV Pt Yrs=254	All Doses Pt Yrs=687
Any SAE	348.6	189.9	204.5	203.7
Asthma	193.7	61.0	94.4	87.3
Pneumonia	10.6	6.8	3.9	5.8
Nephrolithiasis	10.6	6.8	0	1.5
Bronchitis	7.0	0	3.9	1.5
Lobar pneumonia	3.5	0	7.9	2.9
Tendon rupture	3.5	0	3.9	2.9
Atrial flutter	3.5	6.8	0	1.5
Cerebrovascular accident	7.0	0	0	0
Herpes zoster	0	13.6	0	2.9
Hypersensitivity	3.5	6.8	0	1.5
Hypertension	0	0	3.9	2.9
Myocardial ischemia	0	0	3.9	2.9
Viral URTI[1]	3.5	0	3.9	1.5

1. URTI = upper respiratory tract infection
2. Numbers represent the frequency of an event per 1000 patient-years of exposure

OLE Studies

In the OLE studies, the overall incidence of non-fatal SAEs (8% in Study 661 and 9% in Study 666) and the most frequent non-fatal SAE (asthma: 4% in Study 661 and 5% in Study 666) was similar to the RCT Studies.

6.7. Adverse Events Leading to Withdrawal from Investigational Product/Study

RCT Studies

Few withdrawals due to AEs occurred in the RCT Studies (3% in placebo and 3% in mepolizumab [all doses]) (Table 28). All individual AEs leading to withdrawal occurred at an incidence of <1%. The most frequent AEs leading to withdrawal were asthma (3 patients in the placebo group and 4 in the mepolizumab group) and hypersensitivity (2 patients in the placebo group and 3 in the mepolizumab group).

Table 28 Adverse Events Leading to Discontinuation of Study Drug or Withdrawal from the Study Occurring in More than One Patient (RCT Studies, Safety Population)

	Number (%) of Patients			
		Mepolizumab		
AE Leading to Withdrawal (Preferred Term)	Placebo N=412	100 SC N=263	75 IV N=344	All Doses N=915
Any AE leading to WD	12 (3)	3 (1)	4 (1)	23 (3)
Asthma	3 (<1)	0	1 (<1)	4 (<1)
Hypersensitivity	2 (<1)	0	0	3 (<1)
Arthralgia	0	0	1 (<1)	2 (<1)
Liver function test abnormal	1 (<1)	0	1 (<1)	1 (<1)
	Exposure Adjusted[1]			
	Placebo Pt Yrs =284	100 SC Pt Yrs =147	75 IV Pt Yrs =254	All Doses Pt Yrs =687
Any AE leading to WD	45.8	20.3	19.7	37.8
Asthma	10.6	0	3.9	5.8
Hypersensitivity	7.0	0	0	4.4
Arthralgia	0	0	3.9	2.9
Liver function test abnormal	3.5	0	3.9	1.5

1. Numbers represent the frequency of an event per 1000 patient-years of exposure

OLE Studies

Similar to the RCT Studies, withdrawals due to AEs occurred at a low incidence in the OLE studies (1% in Study 661 and 2% in Study 666). AEs which led to withdrawal of more than one patient were asthma, fatigue, and headache (2 patients, <1% each).

6.8. Deaths

As of the October 27, 2014 data cut-off date for the 120 Day Safety Update, 6 deaths had been reported in the severe eosinophilic asthma program (Table 29). Since October 27, 2014, GSK has been notified of the death of two additional patients enrolled in OLE Study 666.

Table 29 Deaths (RCT and OLE Studies, Safety Population)

Cause of Death	Treatment
Randomized Controlled Trials	
Road traffic accident	Placebo
Asthma exacerbation/Sepsis/GI hemorrhage/Aspiration	Placebo
Severe acute asthma exacerbation resulting in brain hypoxia	Mepolizumab 250 mg IV
Acute pancreatitis related to biliary microlithiasis	Mepolizumab 250 mg IV
Suicide	Mepolizumab 750 mg IV
Open-Label Extension Studies	
Asthma exacerbation	Mepolizumab 100 mg SC
Acute cardiac failure[1]	Mepolizumab 100 mg SC
Complications from morbid obesity[1]	Mepolizumab 100 mg SC

1. Reported after data cut-off for 120 Day Safety Update

RCT Studies

Five deaths were reported in the RCT Studies: 2 patients (<1%) treated with placebo and 3 patients (<1%) treated with mepolizumab; none was considered related to study medication by the investigator.

Placebo

- A 51-year-old male patient in Study 588 died due to a traffic accident. The patient had received a total of 8 doses of placebo prior to his death.
- A 38-year-old female patient in Study 575 was hospitalized due to a severe asthma exacerbation. She developed severe sepsis and subsequent GI bleeding and aspiration, which led to death. The patient had received 6 injections of placebo prior to onset of these SAEs. The GI bleeding was considered by the investigator as possibly due to the concomitant medication, voriconazole.

Mepolizumab

- A 60-year-old female patient in Study 997, experienced fatal SAEs of severe acute pancreatitis and septic shock, 225 and 286 days after the first dose of mepolizumab 250 mg IV, respectively and 1 day after the most recent and last dose. The patient was hospitalized; severe biliary microlithiasis was subsequently diagnosed followed by a mesenteric thrombosis. The patient's condition continued to deteriorate and she developed septic shock which led to a fatal outcome. The investigator considered the events of pancreatitis and septic shock possibly related to biliary tract lithiasis, which was undiagnosed prior to the onset of pancreatitis.
- A 56-year-old female in Study 997 with a prior history of ICU admissions due to severe uncontrolled asthma (the most recent occurred within months of this event and required intubation), experienced a fatal SAE of severe acute asthma exacerbation approximately 11 hours after receiving the second infusion of mepolizumab 250 mg IV. Upon arrival at the emergency department, the patient was unconscious and rapidly progressed to a cardiopulmonary arrest requiring

resuscitation. The patient had rapid cardiovascular and respiratory recovery, but remained in a coma. Supportive treatment was stopped after a brain MRI revealed multiple and extensive ischemic lesions due to severe hypoxia and the patient died. The event was judged by the investigator to be possibly due to the patient's underlying extremely severe and unpredictable asthma. The investigator reported that the patient had "absolutely uncontrollable" disease despite all therapies received previously and was enrolled into Study 997 "as a last resort" for finding an effective treatment to control her disease.

- A 54-year-old male patient in Study 997, experienced a fatal SAE of severe asphyxia due to suicide by hanging 298 days after his first dose of mepolizumab 750 mg IV and 19 days after the last dose. The patient had no previous history of depression.

OLE Studies

Three deaths were reported from OLE Studies; all were considered unrelated to treatment with mepolizumab by the investigators.

- A 29-year-old male in Study 666 developed a severe respiratory arrest 244 days after the first dose of mepolizumab 100 mg SC and 21 days after the last dose. The patient was hospitalized and died 6 days after being admitted to the hospital. The investigator reported that the death was not sudden and resuscitation was not attempted due to a 'Do Not Resuscitate' order. The event was judged by the investigator to be due to his underlying asthma and increased risk for death due to severity of the disease.
- A 64-year-old male subject experienced acute cardiac failure approximately 19 months after the first dose of mepolizumab 100 mg SC and 8 days after the most recent dose. The subject was found not breathing at home and pronounced dead in the emergency department. An autopsy was performed and the cause of death was reported as acute heart failure subsequent to coronary artery disease. The investigator considered that there was no reasonable possibility that the event may have been caused by mepolizumab.
- A 34-year-old male in Study 666 experienced complications due to morbid obesity and died approximately 2.3 years since the first dose of mepolizumab and 15 days after the most recent dose. The patient awoke in the night to use the bathroom after which he told his partner to call an ambulance and then collapsed. Attempts to resuscitate by ambulance staff were unsuccessful. An autopsy was not performed; the patient was cremated. Cause of death as per the coroner and the event reported to GSK was 'complications due to morbid obesity', which the investigator assessed as unrelated to treatment with mepolizumab. This is a recent report and pursuit of additional follow-up details is in progress.

6.9. Safety in Subgroups

For the demographic subgroups examined, the profile of SAEs was generally similar to the overall population. Although some subgroups were small, there did not appear to be treatment- or dose-related effects on the incidence of SAEs by age or race (Table 30).

Table 30 Serious Adverse Events by Demographic Subgroups (RCT Studies, Safety Population)

SAEs, n/N (%)	Placebo	Mepolizumab		
		100 mg SC	75 mg IV	All Doses
Any SAE	**63/412 (15)**	**17/263 (6)**	**34/344 (10)**	**92/915 (10)**
Age				
12-17 years	2/9 (22)	1/9 (11)	0/9	2/19 (11)
18-64 years	55/366 (15)	13/216 (6)	32/302 (11)	84/814 (10)
≥65 years	6/37 (16)	3/38 (8)	2/33 (6)	6/82 (7)
Race				
African American/Heritage	3/9 (33)	3/7 (43)	2/11 (18)	8/30 (27)
White	49/349 (14)	8/219 (4)	28/288 (10)	72/783 (9)
Asian	11/49 (22)	6/35 (17)	4/43 (9)	12/95 (13)
Other	0/5	0/2	0/2	0/7
Gender				
Female	38/234 (16)	12/160 (8)	25/209 (12)	65/555 (12)
Male	25/178 (14)	5/103 (5)	9/135 (7)	27/360 (8)

6.10. Long-term Safety

Examination of AEs by time to onset for the RCT and OLE studies (presented in the BLA) showed no increase in incidence or type of AEs as treatment exposure increased.

As of the data cut-off date for the 120 Day Safety Update (October 27, 2014), the total exposure to mepolizumab in the severe asthma studies, regardless of dose or route, was 1866.22 patient-years with a median duration of exposure of 18.2 months and a maximum of 36 months. The profile of AEs, including AEs of special interest (Table 31), in the OLE studies remains consistent with that reported in the BLA for the 100 mg SC group in the RCT studies.

AEs in the Infections and infestations SOC were most frequent, primarily nasopharyngitis (31%), URTI (16%), bronchitis (12%), and sinusitis (10%) and the incidence was similar between the two studies. The incidence of serious opportunistic infections and malignancies in the OLE Studies remain consistent with the incidence reported from the RCT Studies and are not suggestive of immunosuppression occurring over time as exposure increases. Similarly, the incidence of other AE of special interest reported in the OLE Studies including hypersensitivity reactions, local injection site reactions, and CVT events remained consistent with that observed in the RCT Studies.

Table 31 Overview of Adverse Events and Adverse Events of Special Interest (OLE Studies, Safety Population)

Adverse Event / Adverse Event of Special Interest	Number (%) of Patients[1] Mepolizumab 100 mg SC		
	Study 666 N=347	Study 661 N=651	Total N=998
Any AE	306 (88)	553 (85)	859 (86)
Any non-fatal SAE	41 (12)	93 (14)	134 (13)
Anaphylaxis	0	0	0
Systemic Reactions	9 (3)	13 (2)	22 (2)
Hypersensitivity	5 (1)	6 (<1)	11 (1)
Non-allergic	4 (1)	7 (1)	11 (1)
Local Injection Site Reaction	37 (11)	27 (4)	64 (6)
Infections	247 (71)	451 (69)	698 (70)
Serious	8 (2)	26 (4)	34 (3)
Opportunistic	3 (<1)	9 (1)	12 (1)
Neoplasms	10 (3)	13 (2)	23 (2)
Malignancies	4 (1)	6 (<1)	10 (1)
Cardiac Disorders	20 (6)	24 (4)	44 (4)
Serious cardiac disorders	2 (<1)	6 (<1)	8 (<1)
Serious CVT[2]	5 (1)	9 (1)	14 (1)

1. Reported as of October 27, 2014
2. CVT = Cardiac, vascular and thromboembolic. In addition to the Cardiac and Vascular SOCs, relevant AEs from other SOCs (e.g., stroke from the Nervous system Disorders SOC) were included for comprehensive summary of all relevant SAEs of CVT nature

6.11. Clinical Laboratory Data

RCT and OLE Studies

No clinically relevant trends or unexpected abnormalities in clinical chemistry or hematology parameters have been observed in the severe eosinophilic asthma clinical program (RCT and OLE studies to date). A few isolated clinical chemistry values of clinical concern (low calcium, low sodium, high/low potassium, high/low glucose) were observed in the RCT and OLE studies, but the incidence of events was similar between placebo- and mepolizumab-treated patients (<1%) and none was considered related to treatment. No patient had a hematology value of potential clinical concern.

Few patients (<1%) had elevated liver function tests that potentially met the protocol-defined stopping liver criteria (3 treated with placebo, 3 treated with 75 mg IV, and none treated with 100 mg SC in the RCT Studies, and 5 treated with 100 mg SC in the OLE studies). Nine of the 11 patients had elevated alanine aminotransferase (ALT), one had elevated aspartate aminotransferase (AST), and the other had elevated gamma glutamyl transferase (GGT); none was associated with an increase in total bilirubin. There was no observed concern with hepatic toxicity, which is consistent with the metabolism of mepolizumab (see Section 9.3.1).

6.12. Electrocardiograms and Vital Signs

RCT Studies

In the RCT Studies, there has been no evidence of QTc prolongation or an increase in ECG abnormalities with mepolizumab. Most patients in the placebo and mepolizumab 100 mg SC and 75 mg IV groups (92% to 93%) had post-baseline corrected QT interval using Fridericia's formula (QTc[F]) values ≤450 msec. The incidence of abnormal, clinically significant ECG findings post-baseline was similar across the placebo and mepolizumab 100 mg SC and 75 mg IV groups (14% to 19%). No treatment effect on heart rate was observed; mean changes from baseline were similar across the placebo and mepolizumab 100 mg SC and 75 mg IV groups (5 to 6 bpm).

In addition, a previous cross-study analysis of ECG QTc data showed that mepolizumab did not adversely affect the QTc interval and the cardiovascular AE profile did not suggest an effect on conduction.

OLE Studies

In the OLE studies, there have been no safety concerns regarding ECGs findings or QTc prolongation.

6.13. Rebound

Adverse event data from the follow-up (8 weeks post last dose) and post-follow-up periods (Study 997, 24 weeks post last dose) of the RCT Studies do not support an exaggerated return of symptoms after cessation of treatment. No verbatim reports of 'rebound' of disease or other AEs indicative of exacerbation of disease have been reported.

A 12-month investigator-supported follow-up study to Study 184 showed that the frequency of severe exacerbations increased after discontinuing mepolizumab [Haldar, 2014]. As expected, eosinophils as well as symptoms and exacerbations returned to baseline (prior to mepolizumab use) between 3 to 6 months after mepolizumab cessation, but these were not considered indicative of rebound. These are expected physiological responses following mepolizumab withdraw.

6.14. Pregnancies

Based on nonclinical data, the risk of pregnancy complications and offspring abnormalities appears to be low.

In all clinical trials, females of child bearing potential must have a negative pregnancy test at screening and agree to use a protocol-specified acceptable contraceptive method consistently and correctly. Few pregnancies (11 patients) have been reported in the severe eosinophilic asthma program as of the October 27, 2014 data cut-off date for the 120 Day Safety Update. Outcomes were known for 9 patients: 3 spontaneous abortions (1 placebo, 1 mepolizumab 75 mg IV, and 1 mepolizumab 100 mg SC), 1 elective termination (mepolizumab 750 mg IV), and 5 full-term healthy infants (3 mepolizumab

75 mg IV and 2 mepolizumab 100 mg SC). Two pregnancies (Study 661) were ongoing as of the data cut-off date of October 27, 2014 for the 120 Day Safety Update.

7. BENEFIT-RISK ASSESSMENT AND CONCLUSIONS

7.1. Therapeutic Justification

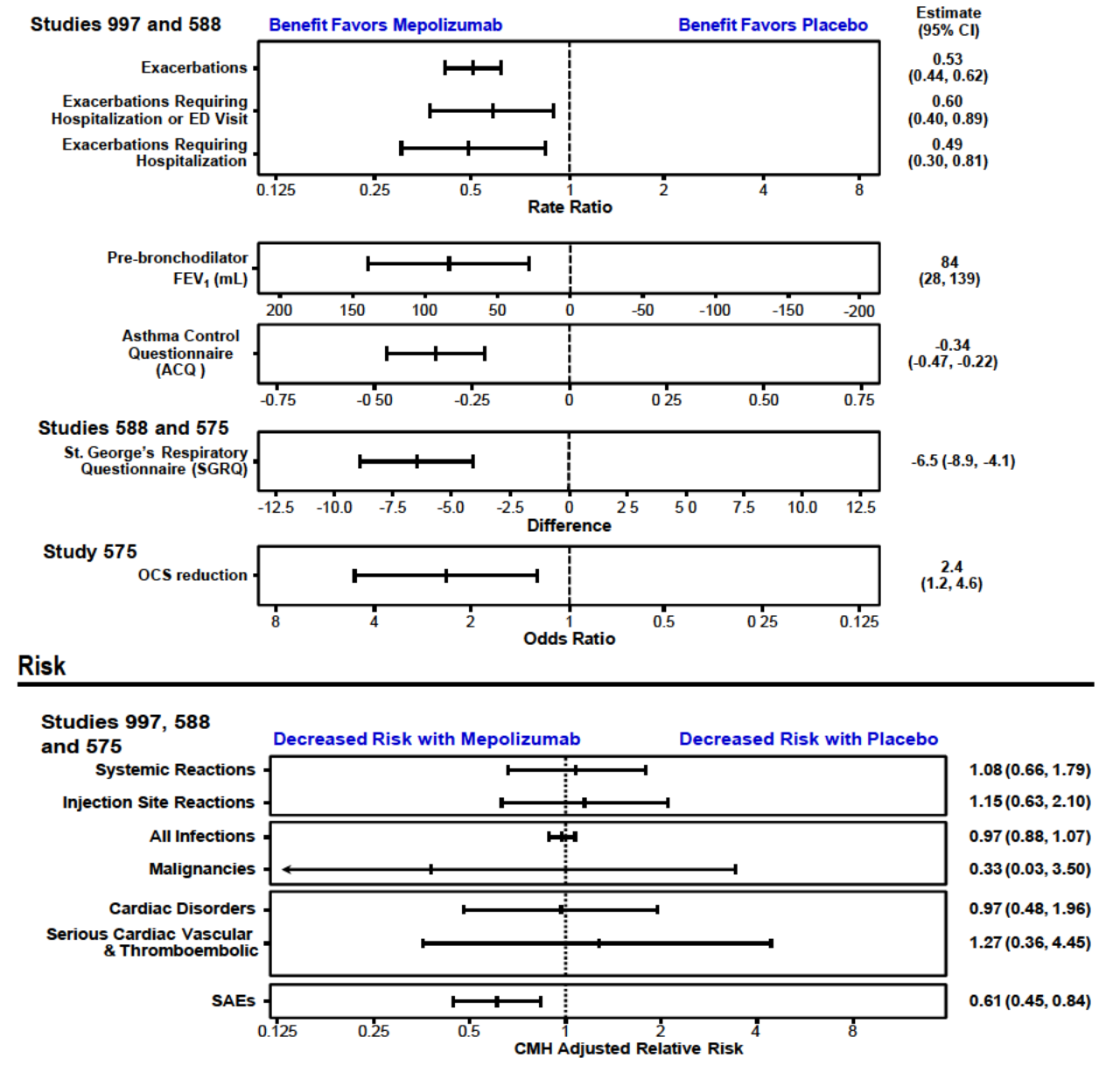
The severe asthmatic population is at a high risk from acute exacerbations and persistent symptoms. Therefore, a critical treatment goal in this population is the reduction of clinically relevant exacerbations and alleviation of symptoms. Additionally, this patient population has a high use of OCS which is accompanied by impactful untoward side-effects and increased risk profile. Due to lack of treatment options, there remains a high unmet need to develop and provide new medications for patients with severe asthma.

Mepolizumab, through its neutralization of IL-5, addresses the need for a specific, effective and well-tolerated treatment in the chronic management of severe eosinophilic asthma. A dose regimen of 100 mg mepolizumab SC once every 4 weeks in addition to standard of care is recommended based on the favorable benefit-risk profile and PD effect of this dose in lowering blood eosinophil counts. In addition to the effect of mepolizumab on exacerbation reduction, the ability to reduce the levels of oral steroid use and consequential burden is considered to be a standalone beneficial outcome for these patients.

7.2. Assessment of Benefits and Risks

Mepolizumab has demonstrated a positive benefit-to-risk profile (Figure 21). Over the duration of the studies, the clinical benefits were maintained and the safety observations remained consistent.

Figure 21 Overall Benefit Risk Profile



Compared with standard of care alone (placebo), add on treatment with mepolizumab is efficacious in patients with severe eosinophilic asthma as demonstrated by statistically significant and/or clinically relevant:

- **Reductions in the frequency of exacerbations that require healthcare utilization:** Robust decreases in asthma exacerbations, exacerbations requiring hospitalizations *or* ED visits, and exacerbations requiring hospitalization only. The reduction of severe asthma exacerbations could potentially lead to reductions in morbidity and fatal events due to asthma.

- **Improvements in lung function:** Any improvements in lung function are of particular clinical importance in this population of patients on maximal asthma therapy including high dose ICS and/or OCS plus a controller medication.
- **Improvements in asthma control:** Patients achieved asthma control with the addition of mepolizumab. In Study 575 while patients were reducing their daily dose of prednisone, the mean improvement in ACQ-5 with mepolizumab compared with placebo exceeded the MCID.
- **Improvements in quality of life:** In Studies 588 and 575, the changes in SGRQ score exceeded the MCID for this instrument indicating marked improvement in asthma symptoms and ability of perform daily activities.
- **Reduction in daily OCS dose:** In Study 575, treatment with mepolizumab 100 mg SC allowed OCS-dependant patients to significantly reduce their daily dose of prednisone without experiencing loss of asthma control. At the end of the treatment period, the median daily dose of OCS was reduced from 10 mg to 3.1 mg in the mepolizumab group, but only from 12.5 mg to 10 mg in the placebo group.

Based on the experience with mepolizumab in the severe eosinophilic asthma clinical program to date, the safety profile is favorable based on the following observations:

- **Overall safety:** The safety and tolerability of mepolizumab plus standard of care has been similar to placebo plus standard of care except for an increase in local injection site reactions with SC administration (8% vs. 3%). The safety profile of mepolizumab 100 mg SC, the dose recommended in the labeling, was similar to the integrated safety profile observed across a 10-fold dose range for mepolizumab (75 mg to 750 mg IV).
- **Adverse events of special interest:** The overall risk of systemic allergic and non-allergic reactions, immunogenicity, infections (including serious and opportunistic), malignancies, and CV disorders (including QTc prolongation) is low. The incidence of these events with mepolizumab plus standard of care was similar to placebo plus standard of care.

7.3. Overall Benefit Risk Conclusions

The safety and efficacy data provide strong evidence of drug effectiveness, a well-characterized safety profile, and overall positive benefit to risk profile for mepolizumab 100 mg SC as an add-on treatment for severe eosinophilic asthma and fully support the intended patient population and the proposed labeling.

The unmet need in patients with severe asthma is clearly recognized [Chung, 2014; GINA, 2013]. Severe asthma reduces the social, financial and health outcomes for people with the disease. Patients with severe asthma have a noticeable impact on the health care system. Severe asthma is generally poorly understood and diagnosed, and inconsistently managed by healthcare providers. A recent study of over 2500 patients reported that the rate of exacerbations was relatively unchanged over a 5 year period in patients with severe asthma despite receiving high-intensity anti-asthma treatment (high dose ICS plus additional controllers) [Schatz, 2014]. These data highlight the persistency

of risk and impairment in this subgroup of patients with severe asthma. It is estimated that up to 50% of total asthma cost is associated with the higher level of morbidity experienced in patients with severe asthma despite the fact that severe asthma represents only 5% to 10% of all patients with asthma [Cisternas, 2003].

The primary benefits of mepolizumab treatment can be classified as (1) reduction/ elimination of exacerbations and (2) the ability to maintain or improve overall asthma control while reducing dependence on daily doses of systemic corticosteroids which are associated with both untoward short- and long-term adverse events.

The exacerbation benefit of mepolizumab treatment in addition to standard of care has been conclusively demonstrated across two long-term studies and has been consistently reported as approximately a 50% reduction (53% for 100 mg SC; 47% and 48% for 75 mg IV) in the annualized rate of exacerbations compared with placebo plus standard of care. To put a 50% reduction in the rate of exacerbations into context, independent meta-analysis by the Cochrane Airways Group [Gibson, 2007] reported that patients with uncontrolled asthma dependent on ICS can expect a 20% reduction in the rate of exacerbations with the addition of LABA, and the addition of omalizumab in exacerbating patients on high-dose ICS plus LABA, the population most similar to the mepolizumab population, achieves approximately a 25% reduction in exacerbations.

Standard of care in the mepolizumab patient population with severe asthma consisted of high dose ICS plus an additional controller with or without regular systemic steroids. This benefit of mepolizumab has been demonstrated in well-controlled studies that emphasize adherence to standard of care medication regimens and provide a rigorous clinical intervention every 4 weeks, likely representing the optimal response for patients receiving standard of care. These studies targeted uncontrolled patients in GINA Steps 4 and 5. For context, in studies 997 and 588 there were a total of 776 and 446 confirmed exacerbations respectively, with 288 and 216 in the placebo arms of each trial respectively. Compared with optimized standard of care treatment plus placebo over 52 weeks, mepolizumab reduced the exacerbation risk by 47% and 50% in Studies 997 and 588, respectively. In other words, this risk reduction equates to 135 and 108 fewer exacerbations experienced for a similar group of patients in Studies 997 and 588.

Importantly, the reduction in exacerbation risk associated with mepolizumab extends equally to the most severe exacerbations, those events requiring ED visits or in-hospital intervention. Treatment with mepolizumab consistently reduced these more severe events by approximately 50% (61% for 100 mg SC; 60% and 32% for 75 mg IV). Chronic inflammation and exacerbations are thought to be associated with an increased risk of permanent damage to the lung tissue or remodeling changes [Bai, 2007]. Thus, it is paramount to control inflammation and reduce exacerbations in patients at high risk. Mepolizumab specifically targets such a high risk population and reduces exacerbations.

Improvements in lung function and quality of life were not consistently demonstrated to be statistically significant across the development program. The AQLQ was used in Study 997; statistically significant results were observed in only one of three active doses. The SGRQ was subsequently selected for its emphasis on disease impact in patients with exacerbating severe asthma [Kupczek, 2013]. The positive effect of mepolizumab on

quality of life using this instrument was demonstrated in studies 588 and 575; this effect was further supported by the favorable findings in the clinician and patient global response to therapy assessment in these studies suggesting that SGRQ may be more suitable for measuring impacted quality of life domains in severe asthma. Compared with Study 997, there was greater improvement in FEV_1 in the 588 and 575 studies. The reason for this is not completely clear but one possibility is that this could be due to having better defined specific hematologic and clinical markers to select patients most likely to respond to mepolizumab treatment.

In Study 575, compared with standard of care, a greater proportion of patients receiving mepolizumab reduced the daily requirement for systemic steroids while maintaining or improving asthma control. The need to protect patients from physiologically active doses of systemic steroids due to the established short- and long-term adverse event profile is a broad-based public health goal. According to asthma guidelines "The aim of treatment should be to control asthma on the lowest dose of OCS possible" [NIH, 2007]. Further, global guidelines specify "OCS should be administered at the lowest effective dose" [GINA, 2013].

Although data are limited evaluating the harmful effects of OCS in patients with asthma, a recent study by Lefebvre and colleagues[Lefebvre, 2015] reported that patients with exposure greater than 6 mg/day had higher risk for developing cardiovascular, infections, and gastrointestinal complications compared with patients with low steroid (≤6 mg/day) exposure. It is noteworthy that in studies 997 and 588, nearly a third of patients were receiving daily OCS and the average dose of prednisone was 10 mg. Thus there is an unmet need to reduce the dose and dependency on OCS in patients with asthma.

In Study 575, 54% of mepolizumab-treated patients achieved a reduction of OCS to less than 5 mg per day compared with 32% of patients receiving placebo. Specifically, after completion of the optimization phase, patients were controlled with a median daily prednisone dose of 12.5 mg in the placebo group and 10 mg in the mepolizumab group. At the end of the study, patients who completed the study were able to reduce their prednisone dose to a median of 10 mg in the placebo group and a median of 3.1 mg in the mepolizumab group. The clinical benefit of such a reduction could impact a large number of patients with severe asthma recognizing that 25% to 50% of patients in the target population of mepolizumab are receiving daily doses of OCS (Studies 184, 997, 588). It is also important to note that the addition of mepolizumab to standard of care, compared with standard of care plus placebo, resulted in statistically improved asthma control and quality of life surpassing the MCID (ACQ-5 and SGRQ) for these instruments despite receiving lower mean doses of OCS.

Patients with severe eosinophilic airway disease represent a significant challenge for clinicians. Oral corticosteroids, the only available treatment for these patients, can lead to serious and often irreversible side effects and complications. For this reason, patients often use lower maintenance doses than required to completely suppress their symptoms [Robinson, 2003; Gamble, 2009]. Study 575 mitigated this clinical dilemma by establishing the minimally effective dose of OCS required for controlling asthma during the Optimization Phase prior to randomization. Study 575 convincingly shows that mepolizumab is an effective and safe treatment for a definable group of patients with an

important unmet need. Reduction of steroid burden is critical for subgroups such as adolescents, and patients with diabetes, hypertension, or dyslipidemia.

Overall, the safety profile of 100 mg SC is comparable to placebo. However, the incidence of local site reactions when administered as a SC dose is higher. Reassuringly, the rate is low (8% for mepolizumab vs. 3% for placebo) and this experience is generally mild, transient, managed with routine supportive care and did not generally result in discontinuation of study medication. Mepolizumab has low immunogenic potential (6%) and most ADAs were transient, the majority occurring only after the first administered dose. In addition, other adverse events of special interest (i.e., hypersensitivity, malignancy, CV events, and infections) have not been associated with an increased risk following mepolizumab treatment from either the RCT Studies or with longer exposure as observed from the OLE Studies. Anaphylaxis has not been associated with mepolizumab treatment. However, it should be noted that rare events, such as anaphylaxis, may not be detectable within the scope of a Phase III program and will continue to be monitored through post-marketing surveillance.

Based on the well-documented positive benefit to risk profile, the limitations associated with current therapeutic treatment options, and the significant morbidity experienced by patients with severe eosinophilic asthma, there is an urgent medical need for additional therapeutic options. Based on the data generated in this clinical development program, GSK believes that the registration of mepolizumab will provide a significant advance in the treatment of patients with severe eosinophilic asthma.

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9. APPENDICES

9.1. Study 575 OCS Titration Algorithms

In Study 575, prednisone/prednisolone adjustments during the OCS Optimization Phase were made based on the titration schedule described in Table 32.

Table 32 OCS Optimization Titration Schedule (Study 575)

Sequential Time Course	Prednisone/Prednisolone Optimization Phase								
	Oral Corticosteroid Dose (mg/day)								
Visit 2 starting dose	35	30	25	20	15	12.5	10.0	7.5	5.0
1st dose reduction (Visit 2)	30.0	25.0	20.0	15.0	12.5	10.0	7.5	5.0	5.0
+ 1 Week	25.0	20.0	15.0	12.5	10.0	7.5	5.0		
+ 1 Week	20.0	15.0	12.5	10.0	7.5	5.0			
+ 1 Week	15.0	12.5	10.0	7.5	5.0				
+ 1 Week	12.5	10.0	7.5	5.0					
+ 1 Week	10.0	7.5	5.0						
+ 1 Week	7.5	5.0							
+1 Week	5.0								

The prednisone titration schedule outlined for the OCS Reduction Phase (Table 33) had larger dose steps and longer duration between steps (i.e., 4 weeks) compared with the schedule outlined for the OCS Optimization Phase (Table 32). The longer duration between dose steps was implemented since it was anticipated that the magnitude of the decrease in the OCS dose during the OCS Reduction Phase would be greater than that during the OCS Optimization Phase. The 4-week timeframe allowed for carryover effects from the prior dose to be minimized and also minimized the risk for adrenal insufficiency complications.

Table 33 OCS Reduction Phase Titration Schedule (Study 575)

Sequential Time Course	Prednisone/Prednisolone Reduction Phase								
	Oral Corticosteroid Dose (mg/day)								
Optimized OCS dose	35	30	25	20	15	12.5	10.0	7.5	5.0
1st dose reduction	25.0	20.0	15.0	10.0	10.0	10.0	5.0	5.0	2.5
+ 4 Weeks	15.0	10.0	10.0	5.0	5.0	5.0	2.5	2.5	1.25*
+ 4 Weeks	10.0	5.0	5.0	2.5	2.5	2.5	1.25*	1.25*	0
+ 4 Weeks	5.0	2.5	2.5	1.25*	1.25*	1.25*	0	0	0
+ 4 Weeks	2.5	2.5	2.5	0	0	0	0	0	0

1. *Patient taking 1.25mg/day should take this as 2.5mg administered every other day

9.2. Statistical Analyses of Efficacy Endpoints

Efficacy analyses were performed on the Intent-to-Treat (ITT) Population which consisted of all randomized patients who received at least one dose of study medication.

Asthma Exacerbations: The rate of exacerbations (primary efficacy endpoint) was compared across groups using a negative binomial model, including covariates for treatment, use of maintenance OCS, region, number of exacerbations in the prior year, and baseline percent predicted FEV_1. This model assumed that missing data was missing at random (MAR). To examine the sensitivity of the results of the primary analysis to departures from this assumption, further sensitivity analyses were performed using multiple imputation methods based on pattern mixture models [Keene, 2014]. This approach models the missing data for the mepolizumab treatment arm based on the results of the placebo arm. The assumptions used to impute the missing part of the data for patients who withdrew early were as follows:

- Jump to Reference: Missing counts were imputed conditional upon the patient's own observed number of events prior to withdrawal. The impact of sampling from this conditional distribution was that if their event rate prior to withdrawal was worse than would be expected (positive residual) on mepolizumab, their imputed event rate after withdrawal would be worse than the expected event rate on placebo. Missing data in the placebo arm were imputed under randomized-arm MAR.
- Unconditional Reference: The basis of this approach was that withdrawal from mepolizumab represented a new episode for the patient and the previous history of events was not used in the imputation model for events post-withdrawal. Instead, missing events for mepolizumab were imputed using the overall mean for placebo, conditional only on baseline covariates. Missing data in the placebo arm were again imputed under randomized-arm MAR.

The rate of exacerbations requiring hospitalization (including intubation and admittance to an ICU) and/or ED visits and the rate of exacerbations requiring hospitalization were analyzed using the same analysis model as used for the primary efficacy endpoint.

FEV_1: Change from baseline in FEV_1 was analyzed using a mixed model repeated measures (MMRM) analysis adjusting for covariates of baseline FEV_1, region, baseline maintenance OCS therapy (OCS vs. no OCS), exacerbations in the year prior to the study (as an ordinal variable), treatment group and visit, plus interaction terms for visit by baseline and visit by treatment group. With MMRM analyses, data from all patients (with at least one post-baseline measure) contribute towards the estimate at each time point even if they had no value at a given time point. The model was used to estimate treatment differences and associated p-values and 95% confidence limits.

Asthma Control: Different versions of the ACQ [Juniper, 2005] were used in Study 997(ACQ-6) and Study 588 (ACQ-5), with the former using the ACQ-6 and the latter ACQ-5. To enable a meta-analysis of the data from these two studies, only questions regarding symptoms collected in Study 997 were used to calculate an ACQ-5 (symptom score) for that study.

Change from baseline was analyzed using an MMRM analysis adjusting for covariates of baseline ACQ symptom score, region, baseline maintenance OCS therapy (OCS vs. no OCS), baseline percent predicted pre-bronchodilator FEV_1, exacerbations documented in the year prior to the study (as an ordinal variable), treatment group and visit, plus interaction terms for visit by baseline and visit by treatment group. Study was included as a covariate in the meta-analysis. The model was used to estimate treatment differences and associated p-values and 95% confidence limits.

Quality of Life: Change from baseline in St. Georges Respiratory Questionnaire (SGRQ) score was analyzed using analysis of covariance adjusting for baseline SGRQ, baseline maintenance OCS therapy, region, and other covariates specific for the exacerbation study 588 or OCS reduction study 575).

In Study 997, Asthma Quality of Life Questionnaire (AQLQ) scores were analyzed using mixed effect repeated measures models adjusting for baseline maintenance OCS therapy, region, baseline AQLQ and visit, plus interaction terms for visit by baseline and visit by treatment group.

Response to Therapy: Patient and clinician rated response to therapy was analyzed using a proportional odds model (multinomial, ordered, logistic model), with covariates of treatment group, region, baseline maintenance OCS therapy (OCS vs. no OCS), exacerbations in the year prior to the study (as an ordinal variable), and baseline percent predicted pre-bronchodilator FEV_1. Study was included as a covariate in the meta-analysis. The model estimates the odds ratio (OR) (mepolizumab/ placebo) of a patient's outcome being in a better (greater improvement) category. Within this analysis, patients with missing responses were included in the 'significantly worse' category. This was a post-hoc analysis.

OCS Reduction: The primary endpoint of the OCS reduction study 575 was the number of patients in each category of percent reduction of OCS dose during Weeks 20-24 compared with the baseline dose (90% to 100% reduction, 75% to <90%, 50% to <75%, >0% to <50%, and a final category of no decrease in OCS or lack of control during Weeks 20-24 or withdrawal from treatment). This was analyzed using a proportional odds model (ordered logistic regression analysis) with covariates of treatment, region, duration of OCS use at baseline (<5 years vs. ≥5 years), and dose of OCS at baseline (optimized dose).

Blood Eosinophils: Blood eosinophil values below the lower limit of quantification were imputed as half the lower limit of quantification for analysis. Data was log-transformed prior to analysis. Ratios to baseline were analyzed within each of the studies using an MMRM analysis adjusting for covariates of baseline eosinophil level, region (as defined in the individual study), baseline maintenance OCS therapy (OCS vs. no OCS), baseline percent predicted pre-bronchodilator FEV_1, exacerbations in the year prior to the study (as an ordinal variable), treatment group and visit, plus interaction terms for visit by baseline and visit by treatment group. The model was used to estimate the treatment differences and associated p-values and 95% confidence limits.

Control for Multiplicity: For studies 997 and 588, a closed testing procedure was used within each study to ensure strong control of the type I error in adjusting for multiplicity across treatment comparisons and primary and secondary endpoints.

In Study 997, following an initial test for a linear trend of decrease in exacerbation rate with increasing dose of mepolizumab, each dose of mepolizumab (75, 250, and 750 mg IV) was compared with placebo using a one-sided Hochberg testing procedure with a one-sided α=2.5%. In Study 588 each dose (75 mg IV and 100 mg SC) was compared with placebo using a one-sided Hochberg testing procedure with a one-sided α=2.5%.

In both studies a hierarchical 'gatekeeping' approach was used to control for multiplicity arising from the testing of the primary and secondary endpoints. A step-down testing procedure was applied where inference for an endpoint in the predefined hierarchy was dependent on statistical significance having been achieved for the previous endpoints in the hierarchy. For each endpoint, multiplicity across different treatment comparisons was controlled using the one-sided Hochberg testing procedure.

The hierarchy of endpoints in each study was defined as follows:

Study 997

1. Rate of exacerbations (primary endpoint)
2. FEV_1 pre-bronchodilator at Week 52
3. Asthma Quality of Life Questionnaire (AQLQ) score at Week 52
4. Rate of exacerbations requiring hospitalizations and/or ED visits
5. ACQ score at Week 52

Study 588

1. Rate of exacerbations (primary endpoint)
2. Rate of exacerbations requiring hospitalization and/or ED visits
3. Rate of exacerbations requiring hospitalization
4. Change from baseline in clinic pre-bronchodilator FEV_1 at Week 32
5. Change from baseline in St. George's Respiratory Questionnaire (SGRQ) score at Week 32

Differences in the rates of exacerbations (primary endpoint) were significant after adjustment for all comparisons of mepolizumab treatment groups with placebo. In Study 588, the reduction in the rate of exacerbations resulting in an emergency department visit or hospitalization was significant after adjustment for multiple testing (p=0.03) for mepolizumab 100mg SC vs. placebo. Although the hierarchical gatekeeping approach across outcomes dictated that formal analysis was to be stopped before analysis of the remaining secondary outcomes, the value of such adjustments has been questioned [Stone, 2013]. Instead, it has been proposed that expert judgment should be used for the interpretation of secondary outcomes.

9.3. Overview of Clinical Pharmacology

9.3.1. Pharmacokinetics

Mepolizumab is a humanized IgG1 mAb that exhibits dose-proportional and time-independent pharmacokinetics.

The initial phase of mepolizumab clinical development used an IV route of administration which progressed to a SC route due to clear patient and healthcare provider preference. Mepolizumab administered SC, the requested route for approval, is well absorbed with an absolute bioavailability ranging from 74-80%, and aligned with expectations for a mAb targeting a soluble ligand [Keizer, 2010]. Site of injection (abdomen, arm, and thigh) affects absolute bioavailability minimally (64%, 75%, and 71%) [Ortega, 2014].

The use of a SC or IV route of administration obviates the need to investigate the impact of food on mepolizumab exposure.

Mepolizumab SC absorption is slow, with an absolute bioavailability of 74-80%, a time to maximum concentration (Tmax) of 4-8 days, and a distribution half-life of 1-2 days. Mepolizumab distributes into a volume of approximately plasma and interstitial space (55-85 mL/kg) and is catabolized by ubiquitous proteolytic enzymes. Mepolizumab does not undergo target-mediated clearance. Mepolizumab is eliminated with a systemic clearance of 1.9-3.3 mL/day/kg (0.22 L/day for a 70 kg patient or 3.1 mL/day/kg) and has a terminal-phase elimination half-life of 20 days. Mepolizumab has two-fold accumulation following repeat dosing every 4 weeks, consistent with the long half-life. The pharmacokinetics of IV mepolizumab are well-described using a two-compartment model with first-order distribution and elimination. Pharmacokinetic parameter estimates were consistent across studies, diseases and ethnicities, with pediatric pharmacokinetics predictable from adults. Mepolizumab IV exposure in healthy Japanese and Caucasian patients are comparable. Bodyweight was the only covariate found to have a statistically significant effect on both clearance and volume, consistent with allometry seen with other therapeutic proteins. The overall magnitude of effect of bodyweight on exposure was not, however, deemed clinically relevant. This finding mitigated the need for further investigations and dose adjustment in special populations.

Mepolizumab is a mAb with a large molecular weight of 149.2 kDaltons, precluding elimination by glomerular filtration. Consequently, changes in renal function are not anticipated to impact the elimination of mepolizumab. Likewise, since mepolizumab is degraded by widely distributed proteolytic enzymes, not restricted to hepatic tissue, hepatic function does not therefore influence the elimination of mepolizumab. For this reason, no specific renal or hepatic impairment studies were conducted.

Mepolizumab is considered to have a low potential for drug-drug interactions because it selectively binds and neutralizes the cytokine IL-5. There are no reports of IL-5 receptors being expressed on hepatocytes. Neutralization of IL-5 is therefore not expected to alter gene expression of cytochrome P450 or transporters. No formal drug interaction studies have been conducted.

Mepolizumab has a relatively low level of immunogenicity (<6%) that did not show appreciable influence on either PK or PD; as assessed by blood eosinophil count. There was no evidence of a correlation between antibody titers and change in blood eosinophil count.

9.3.2. Pharmacodynamics

The mechanism by which mepolizumab exerts its activity is by binding to human IL-5, preventing IL-5 from binding to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface and thus inhibiting signaling. Mepolizumab binds to IL-5 with nanomolar affinity and specificity. Neutralization of IL-5 leads to a reduction in the production rate and survival of eosinophils which is expected to provide therapeutic benefit in eosinophilic conditions such as severe eosinophilic asthma.

Mepolizumab treatment produces a consistent and sustained reduction in blood eosinophil count whose magnitude and duration is dose-dependent. Mepolizumab also reduces eosinophils in sputum and bone marrow. There are non-linear dose- and concentration-responses to blood eosinophil count. Dose-response is unchanged by administration route, after adjusting for bioavailability. In the PK/PD Study 092, an inhibitory Imax model estimated the SC doses resulting in 50% and 90% of the maximum achievable inhibition (ID_{50} and ID_{90}) to be 11 and 99 mg, respectively. The characterization of the dose-response relationship for blood eosinophil count supported the rationale for the selection of mepolizumab therapeutic dose (100 mg SC) in conjunction with the results of the dose-ranging Phase IIb/III efficacy study (Study 997), by selecting a dose providing 90% of maximum achievable pharmacology. The adequacy of this SC dose was confirmed in the severe asthma Phase III study (Study 588) where similar blood eosinophil reductions were observed at corresponding doses of mepolizumab 75 mg IV and 100 mg SC.

9.3.3. Analytical Methods

The measurement of mepolizumab plasma concentrations in support of the clinical development program was carried out by validated bioanalytical immunoassay methods with a Lower Limit of Quantification of 50 ng/mL. The assay was developed by GSK and then transferred to Alliance Pharma who conducted the sample analysis for the Phase II/III studies. The bioanalytical methods used to measure concentrations of mepolizumab in human plasma were selective, accurate and reproducible. The assay demonstrated tolerance to non-neutralizing anti-drug antibodies (ADAs) up to the maximum titer observed in the PK samples collected during the clinical studies. Underestimated mepolizumab concentration can, however, be expected in the presence of neutralizing ADAs.